UNIVERSITI PUTRA MALAYSIA

ETHNOBOTANICAL STUDY OF ANTICANCER PLANTS USED IN UGBINE, NIGERIA AND BIOACTIVITY-GUIDED ISOLATION OF CYTOTOXIC AGENTS FROM Synclisia scabrida (Miers) ex Oliv

NWAEFULU OGOCHUKWU NGOZI

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

June 2022

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DEDICATION

This work is dedicated to God Almighty; the source of life, all wisdom and knowledge for His immeasurable love and favour towards me.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

ETHNOBOTANICAL STUDY OF ANTICANCER PLANTS USED IN UGBINE, NIGERIA AND BIOACTIVITY-GUIDED ISOLATION OF CYTOTOXIC AGENTS FROM *Synclisia scabrida* (Miers) ex Oliv

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June 2022

Chairman : Professor Johnson Stanslas, PhD
Faculty : Medicine and Health Sciences

Introduction: Plants are promising source of novel anticancer agents. Although many breakthroughs have been made in cancer treatment, it remains suboptimal. Therefore, alternative therapeutics with novel mechanisms of action, with minimal side effects and costs are urgently needed.

Method: Structured questionnaires were used for the ethnobotanical study. The ground whole roots and leaves of *Synclisia scabrida* (Miers) ex Oliv (SS) and leaves of *Petiveria alliacea* L. (PA) were sequentially and separately extracted using a solid–solvent ratio of 1:2, of hexane, dichloromethane, ethyl acetate, methanol, or dichloromethane: methanol (1:1), by cold maceration for 72 h followed by another cold maceration for 24 h. The extract was filtered, concentrated at 40°C with a rotary evaporator and further dried in the oven set at 40°C to obtain crude extracts, which were stored in a refrigerator. A preliminary phytochemical analysis of SS whole root methanol extract was carried out. MTT cell viability assay was employed to evaluate the cytotoxicity potential of the extracts/compounds in colon (HCT-116), prostate (PC-3), breast (MCF-7), pancreatic (PANC-1) cancer cells and human normal lung (BEAS-2B) and murine microglial (BV-2) cells. Cell cycle distribution of treated PANC-1 was analysed by flow cytometry for understanding of the mechanism behind the observed anticancer potential of SS. Using a bioassay-guided approach, the most active extract/fraction were purified to yield 4 active compounds (SS_C1, SS_C2, SS_C3 and SS_C4). The structures of SS_C2 and SS_C4 were successfully characterised using 1H, 13C-NMR, COSY, HMBC, HSQC, FTIR and LC/MS Q-TOF spectroscopy. The compounds' molecular targets were predicted using *in silico* molecular docking and molecular dynamic approaches.

Results: The ethnobotanical study revealed the use of SS and PA for cancer treatment. Phytochemical screening of the methanol extract confirmed the presence of alkaloids, tannins, flavonoids, steroids, and fixed oil. The methanol extract had the following IC_{50}

(µg/mL) in cancer cell lines: HCT-116 (23.3 ± 10.4), MCF-7 (35.0 ± 5.0), PC-3 (29.3 ± 11.0) and PANC-1 (5.7 ± 1.2). SS induced a dose-dependent arrest of PANC-1 cells in the S phase. Structure elucidation of SS_C2 and SS_C4 revealed they are bisbenzylisoquinoline alkaloids. Both compounds were identified as close analogues of cosculine and cycleanine, respectively. SS_C2 (IC_{50} = 46.7 ± 5.8 µg/mL; SI = 2.1; P<0.000) and SS_C4 (IC_{50} = 41.7 ± 7.6 µg/mL; SI = 2.4; P<0.000) were selectively toxic towards HCT-116 and MCF-7, respectively. The selectivity was far greater than that of gemcitabine, which showed higher toxicity to normal lung cells (BEAS-2B). The *in silico* molecular dynamic simulations results showed RMSF plots of PARP1–ligand complexes were more stable than the apo protein. This shows a very high PARP1-ligand complexation stability, suggesting that both ligands (SS_C2 and SS_C4) are potential PARP1 inhibitors.

Conclusion: SS_C1 was active against colon and pancreatic cancers, SS_C2 was selectively active against colon cancer while SS_C4 had the best selectivity towards breast cancer cells. SS_C2 and SS_C4 are new bisbenzylisoquinoline alkaloids, and potential PARP1 inhibitors which could become leads for the development of targeted therapy for the treatment of colon, breast, and pancreatic cancers.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KAJIAN ETNOBOTANI TUMBUHAN ANTIKANSER YANG DIGUNAKAN DI UGBINE, NIGERIA DAN PENGASINGAN BERPANDUKAN BIOAKTIVITI EJEN-EJEN SITOTOSIK DARI *Synclisia scabrida* (Miers) ex Oliv

Oleh

NWAEFULU OGOCHUKWU NGOZI

Jun 2022

Pengerusi : Profesor Johnson Stanslas, PhD
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Pengenalan: Tumbuhan merupakan sumber yang dipercayai mampu dijadikan sebagai agen antikanser baru. Meskipun banyak penemuan dalam rawatan kanser telah berjaya diperkenalkan, namun ia masih di tahap separa optimum. Oleh yang demikian, terapi alternatif bersama mekanisme tindakan baru, dengan kesan sampingan dan kos perbelanjaan yang minimum diperlukan segera.

Kaedah: Soal selidik berstruktur telah diguna pakai bagi tujuan kajian etnobotani. Setiap akar dan daun *Synclisia scabrida* (Miers) ex Oliv (SS) dan juga daun *Petiveria alliacea* L. (PA) diekstrak secara berasingan, mengikut turutan dengan menggunakan nisbah 1:2 bagi pepejal kepada pelarut heksana, diklorometana, etil asetats, metanol, atau diklorometana: metanol (1:1), dengan pemerasan sejuk selama 72 jam diikuti dengan pemerasan sejuk yang seterusnya selama 24 jam. Ekstrak ditapis, dipekatkan pada suhu 40°C dengan menggunakan penyejat berputar dan selanjutnya dikeringkan dalam ketuhar yang ditetapkan pada suhu 40°C untuk mendapatkan ekstrak mentah, yang kemudiannya disimpan di dalam peti sejuk. Analisis fitokimia awal bagi ekstrak metanol akar SS telah dijalankan. Analisis MTT viabiliti sel digunakan untuk menilai potensi sitotoksisiti ekstrak/sebatian dalam sel kanser kolon (HCT-116), prostat (PC-3), payudara (MCF-7), pankreas (PANC-1) dan sel normal paru-paru manusia (BEAS-2B) dan sel mikroglial murin (BV-2). Taburan kitaran sel PANC-1 yang dirawat telah dianalisis menggunakan sitometri aliran untuk mengenalpasti mekanisme di sebalik potensi SS sebagai agen antikanser. Dengan menggunakan pendekatan yang berpandukan biocerakinan, ekstrak/pecahan yang paling aktif telah dimurnikan bagi menghasilkan 4 sebatian aktif (SS_C1, SS_C2, SS_C3 dan SS_C4). Struktur SS_C2 dan SS_C4 telah berjaya dicirikan menggunakan spektroskopi 1H, 13C-NMR, COSY, HMBC, HSQC, FTIR dan LC/MS Q-TOF. Sasaran molekul sebatian telah diramalkan dengan menggunakan pengedokan molekul siliko dan beberapa pendekatan dinamik molekul.

Keputusan: Kajian etnobotani telah menunjukkan kegunaan SS dan PA dalam rawatan kanser. Pemeriksaan fitokimia ekstrak metanol telah mengesahkan kehadiran alkaloid, tanin, flavonoid, steroid, dan minyak lemak. Ekstrak metanol mempunyai IC_{50} (µg/mL) yang berlainan terhadapsetiap sel kanser yang berikut: HCT-116 (23.3 ± 10.4), MCF-7 (35.0 ± 5.0), PC-3 (29.3 ± 11.0) dan PANC-1 (5.7 ± 1.2; $P<0.009$). SS telah membantutkan sel PANC-1 pada fasa S, dengan bergantung kepada dos. Penjelasan struktur SS_C2 dan SS_C4 telah mendedahkan bahawa ia adalah alkaloid bisbenzylisoquinoline. Kedua-dua sebatian telah dikenal pasti sebagai analog rapat cosculine dan cyclanine. Secara selektifnya, kesan toksik telah diperlihatkan oleh SS_C2 (IC_{50} = 46.7 ± 5.8 µg/mL; SI = 2.1; $P<0.000$) terhadap HCT-116 manakala SS_C4 (IC_{50} = 41.7 ± 7.6 µg/mL; SI = 2.4; $P<0.000$) terhadap MCF-7. Selektiviti tersebut adalah jauh lebih besar daripada gemcitabine, yang menunjukkan ketoksikan yang lebih tinggi kepada sel paru-paru normal (BEAS-2B). Keputusan simulasi dinamik molekul dalam siliko menunjukkan plot RMSF kompleks PARP1-ligan lebih stabil berbanding protein apo. Ini menunjukkan kestabilan kompleksasi PARP1-ligan yang sangat tinggi, seterusnya mencadangkan bahawa kedua-dua ligan (SS_C2 dan SS_C4) berpotensi sebagai perencat PARP1.

Kesimpulan: SS_C1 aktif terhadap kanser kolon dan pankreas, SS_C2 aktif secara selektif terhadap kanser kolon manakala SS_C4 mempunyai selektiviti terbaik terhadap sel kanser payudara. SS_C2 dan SS_C4 ialah alkaloid bisbenzylisoquinoline baharu dan berpotensi sebagai perencat PARP1 yang mampu menjadi peneraju untuk perkembangan terapi bersasar untuk rawatan kanser kolon, payudara dan pankreas.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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%	Percentage
°C	Degree Celsius
H	Hour
Nm	Nanometre
mg/kg	Milligram per kilogram
km^2	Square kilometre
G	Gram
w/w	Weight per weight
mL	Millilitre
mL/min	Millilitre per minute
U/mL	Unit per millilitre
µg/mL	Microgram per millilitre
v/v	Volume per volume
µL	Microlitre
µM	Micromolar
<	Less than
>	Greater than
Bar	Metric unit of pressure
Ns	Nanosecond
Å	Angstrom
kcal/mol	Kilocalorie per mole
K	Kelvin
m/z	Mass-to-charge ratio

g/mol	Gram per mol
δ_H	Chemical shift values of ^{1}H-NMR
δ_C	Chemical shift values of ^{13}C-NMR
Ppm	Parts per million
S	Singlet
M	Multiplet
J	Coupling constants
Hz	Hertz
mg/ml	Milligram per millilitre
4T1	Colon cancer cells
^{1}H-NMR	Proton NMR
2D NMR	Two-dimensional NMR
^{13}C-NMR	Carbon-13 NMR
ANOVA	One-way analysis of variance
AR	Androgen receptor
ACHN	Kidney cancer cell
ASTM	American Standard Test Sieve Series
ATP	Adenosine triphosphate
AMBER	Assisted Model Building with Energy Refinement
ATR	Ataxia telangiectasia and Rad3-related protein
AM1-BCC	semi-empirical (AM1) with bond charge correction (BCC)
A2780	Ovarian cancer cells
A549	Lung cancer cells
BEAS-2B	Human lung cells

BER	Base excision repair
BV-2	Murine cells
BBIQ	Bisbenzylisoquinoline
BETT	5-(2-benzofuryl)-4-phenyl-1,2,4-triazole-3-thiol
CFL1	Actin binding factor cofilin
c-Abl	Abelson tyrosine kinase
CDK	Cyclin dependent kinase
COX-2	Cyclooxygenase-2
CAM	Complementary and alternative medicine
CC	Column chromatography
COSY	Correlation spectroscopy
CH_3	Methyl group
CH_2	Methylene group
CH	Methine group
CHK1	Checkpoint kinase 1
CHARMM	Chemistry at Harvard Macromolecular Mechanics
CD_3OD	Deuterated methanol
CD_3COCD_3	Deuterated acetone
DEPT	Distortionless enhancement by polarisation transfer
DNA	Deoxyribonucleic acid
DCM	Dichloromethane
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DS	Discovery Studio

DSB	Double-strand breaks
EDTA	Ethylenediaminetetraacetic acid
ER	Oestrogen receptor
ERK	Extracellular signal-regulated kinase
EA	Ethyl acetate
EGFR	Epidermal growth factor receptor
ESI	Electrospray ionization
FGFR	Fibroblast growth factor receptor
FRIN	Forestry Research Institute of Nigeria
FHI	Forest Herbarium Ibadan
$FeCl_3$	Iron (III) chloride
GAFF	General AMBER Force Field
GLC	Gas-liquid chromatography
GSC	Gas-solid chromatography
GAE	Gallic acid equivalents
HDAC	Histone deacetylases
HCT-15	Colorectal cancer cell
HT-29	Colorectal cancer cell
HX	Hexane
HCT-116	Colorectal cancer cells
HPLC	High-performance liquid chromatography
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum coherence
IL-6	Interleukin-6

IL-23	Interleukin-23
IL-1β	Interleukin 1 beta
iNOS	Inducible nitric oxide synthase
IR	Infrared spectroscopy
IC_{50}	Half maximal inhibitory concentration
IPA	Isopropanol
KRAS	Kirsten rat sarcoma viral oncogene
LOX-IMVI	Melanoma cell
$LIMK1_{CAT}^{D460N}$	LIM Domain Kinase 1 mutant
LC/MS-QTOF	Liquid chromatography-mass spectrometry quadrupole time of flight
miRNAs	MicroRNAs
MHz	Mega Hertz
MD	Molecular dynamics
MeOH	Methanol
MDA-MB-231	Breast cancer cell
MCF-7	Breast cancer cells
MS	Mass spectroscopy
MAPKs	Mitogen-activated protein kinases
MTT	Tetrazolium-based 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
MEK	Mitogen-activated protein kinase
mTOR	Mammalian target of rapamycin
nt	Not tested
na	Not available

nSH3	N-terminal SH3
NaCl	Sodium chloride
NVT	Amount of substance (N), volume (V) and temperature (T) ensemble
NPT	Constant-temperature, constant-pressure ensemble
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NCI-H23	Non-Small Cell Lung Carcinoma
Ovcar-8	Ovarian cancer cells
PKB/Akt	Protein kinase B
PME	Particle Mesh Ewald
PBS	Phosphate buffer saline
PI	Propidium iodide
PA	*Petiveria alliacea* Linnaeus
PDB	Protein Data Bank
PAL	*Petiveria alliacea* leaf
PMF	Potential of mean force
PARG	PARP and poly (ADP-ribose) glycohydrolase
PC-3	Prostate cancer cell
PANC-1	Pancreatic cancer cells
PI3K	Phosphatidylinositol-3-kinase
PDK1	Pyruvate dehydrogenase kinase 1
PTLC	Preparative thin layer chromatography
RAF	Rapidly accelerated fibrosarcoma

Rt	Retention time
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute medium
RMSD	Root mean square deviations
RNase	Ribonuclease
RCSB	Research Collaboratory for Structural Bioinformatics
RMSF	Root mean square fluctuation
SS	S*ynclisia scabrida* (Miers) ex Oliv
SSF	SS fraction
SSM_CF	SS methanol column fraction
SSM_F4–8/CSF/8–21	Column sub-fraction of SS methanol column fraction
SSM_F4–8/CSF/8–21/3/ S2	Column sub-fraction of SS methanol column fraction spot 2
SS_C1	SS compound 1
SS_C2	SS compound 2
SS_C3	SS compound 3
SS_C4	SS compound 4
SI	Selectivity index
SSB	Single-strand breaks
SPSS	Statistical Package for the Social Sciences
SSR	*Synclisia scabrida* root
SSL	*Synclisia scabrida* leaf
STAT3	Signal transducer and activator of transcription 3
SBDD	Structure-based drug design

TLC	Thin-layer chromatography
TPS	Total population sampling
TIC	Total ion chromatogram
UV	Ultraviolet
VMD	Visual molecular dynamics
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organisation

Amino acids

Gly	Glycine
Arg	Arginine
Asp	Aspartic acid
His	Histidine
Tyr	Tyrosine
Met	Methionine
Ile	Isoleucine
Ser	Serine
Glu	Glutamic acid
Phe	Phenylalanine
Ala	Alanine
Asn	Asparagine
Lys	Lysine
Cys	Cysteine
Leu	Leucine

Val	Valine
Gln	Glutamine

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Cancer poses a serious threat to global health, affecting both developed and developing countries. According to the World Health Organisation (WHO) 2020, non-communicable diseases are on the rise and caused 74% of all deaths in the world in 2019 (WHO, 2020). Cancer is a non-communicable disease; in 2020, new cases were estimated to have risen to 19.3 million and new deaths to 10 million globally (Sung et al., 2021). In 2020, cancer became the second leading cause of death in the United States (Siegel et al., 2020). Nevertheless, the cancer load is still alarming, with 1,898,160 new cancer cases and 608,570 cancer deaths estimated to happen in the United States in 2021 (Siegel et al., 2021). There are many types of cancer; globally, the most diagnosed is breast cancer with 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancer (Sung et al., 2021). In 2020, lung cancer was the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancer (Sung et al., 2021).

Breast cancer is the most diagnosed cancer among American women. In 2021, it is estimated around 30% of newly diagnosed cancers in women will be breast cancers (American Cancer Society, 2021). In 2021, 281,550 new cases of invasive breast cancer are estimated in women in the U.S., together with 49,290 new cases of non-invasive (*in situ*) breast cancer, while around 43,600 women in the U.S. are expected to die in 2021 from breast cancer (American Cancer Society, 2021). Because the incidence increases annually by 0.4%, researchers have been challenged to identify new, more effective treatments (Jemal et al., 2017). If detected early, breast cancer patients can undertake breast-sparing surgery (lumpectomy) with radiotherapy or mastectomy to prevent spread (Moo et al., 2016). A common treatment regimen includes doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for four cycles (AC-T). Current treatments include radiotherapy, surgery, and chemotherapeutic agents, which produce many adverse effects including nausea, fatigue, vomiting, weakened immunity, and hair loss (Costa et al., 2020).

Colorectal/colon cancer (CRC) is the second leading cause of death and the third most common malignant tumour globally. In 2018, 1.8 million new CRC cases were reported, out of which 881,000 deaths occurred; these figures accounted for about 10% of new cancer cases and deaths worldwide (Bray et al., 2018). In the early stages, CRC generally shows as an unusual growth on the inner walls of colon epithelial cells which could be removed by surgery when discovered early. Nevertheless, if not treated, the tumour cells spread to other organs, thereby becoming even insensitive to chemotherapy (Gothai et al., 2018).

Prostate cancer is the second most common tumour (following lung cancer) amongst males globally, with 1,276,106 new cases and 358,989 deaths (3.8% of all tumour deaths in men) in 2018 (Ferlay et al., 2019). Globally, as age increases, the incidence and mortality rate also increase, with 66 years taken as the average age at the time of diagnosis (Panigrahi et al., 2019). The early stage is without symptoms and needs little or no drug. However, the most common complaints are painful and recurrent urination, with nocturia. As the disease advances, urinary retention and back pain may occur.

Globally, pancreatic cancer (PaCa) is the seventh leading cause of cancer-related deaths (Rawla et al., 2019). In 2018, PaCa became the fourth leading cause of cancer-related death, in the United States (Soefje, 2019); that was 4.5% of all cancer deaths (Bray et al., 2018). The incidence and mortality rate of PaCa have been reportedly rising for decades, and PaCa is anticipated to be the second leading cause of cancer-related death in the United States in 2030 (Rahib et al., 2014). In the early stage, PaCa is symptomless (De et al., 2014). As it progresses, there is manifestation of nonspecific symptoms like jaundice, light-coloured stool, stomach pain, weight reduction, and weakness (Siegel, et al., 2018). The obtainable evaluation to diagnose PaCa can be nonspecific and may not identify patients at the early stage of the disease (De et al., 2014). Surgery, radiotherapy, and chemotherapy are conventional treatments that have been used to prolong patients' survival and alleviate symptoms.

Cancer treatment had been done with 'orthodox' chemotherapy drugs, for example, alkylating agents, intercalating dugs, topoisomerase inhibitors, antimetabolites, and antimitotic drugs (Meegan & O'Boyle, 2019). While targeted therapies like kinase inhibitors and monoclonal antibodies have also been used in specific types of cancer, not many can be completely cured with the available therapeutic options. Nevertheless, the success of therapy differs greatly depending on the cancer type and the stage of diagnosis (Meegan & O'Boyle, 2019). One of the major problems with anticancer therapy is the appearance of multidrug resistance – which reduces the efficacy - and relapse. Traditional chemotherapeutic agents directly target the DNA of the cell, but the cells counteract this through the development of resistance. Most of these agents are not selectively toxic to tumour cells; hence, manifestation of side effects in normal body tissues and cells is another limitation to their use. The side effects include peripheral neuropathy, bleeding, rash, allergic reaction, intense chills, shortness of breath, pain, prolonged diarrhoea or vomiting, and bloody stool or urine (Anderson & Matey, 2019; Olsen & Naseman, 2019). Furthermore, high costs limit the accessibility of traditional chemotherapeutic agents to the patients who need them, especially those in the rural communities (Meegan & O'Boyle, 2019). Cancer is now the second most costly disease in the United States, after heart disease: there was a cost increase from $124 billion in 2010 to $157 billion in 2020. The incidence of financial difficulty among cancer patients has been reported to be 49% from large meta-analyses (Gordon et al., 2017; Altice et al., 2016). This has become a major challenge in cancer patients and survivors. Therefore, there is an urgent need for a continuous search for new anticancer drugs that are more selective, efficacious, affordable, and safer.

Plant phytochemical constituents and their derivatives are promising alternatives to improve cancer treatment and, hence, patients' quality of life. Therefore, there has been a lot of research regarding traditional herbal medicines, which have a long history of use to treat various diseases. About 80% of the global population has used and continues to use traditional medicines for their primary health care needs (Illamola et al., 2019; Nagai & Kim, 2017). Furthermore, over 60% of drugs approved for cancer treatment have been derived from secondary metabolites of these medicinal plants. The secondary metabolites include alkaloids, glycosides, steroids, and flavonoids, among others (Newman & Cragg, 2020). These has been used greatly by pharmaceutical industries for drug synthesis (Cragg & Pezzuto, 2016; Sharanabasappa et al., 2007). Asian, African, and even developed nations have used medicinal plants in folk medicine.

Oteng et al. (2019) enumerated plants with proven efficacies for the treatment of various diseases. Many plant-derived chemotherapeutic agents have been used in the battle against cancer. They include vincristine (vinca alkaloid), paclitaxel (taxanes), etoposide (podophyllotoxin) (Li et al., 2017). Although the available synthetic drugs are being used, they are still limited due to the problem of resistance and toxicity to normal cells. Therefore, in a bid to discover alternative therapeutic agents for cancer treatment, traditional healers and herbal vendors have been involved to determine the herbs they have used for this purpose. This information may ultimately become a source of lead compounds and will promote the use of herbal medicine in cancer treatment.

The Ugbine community of Edo State, South South Nigeria, has been using herbs to treat cancer within their community without scientific validation. The cross-sectional survey which was conducted among the traditional healers and herbal vendors in the Ugbine community using a validated structured questionnaire, revealed the root of *Synclisia scabrida* (Miers) (local name: *omonuku*), belonging to the family Menispermaceae is the most effective and common herb used for treatment of cancer. *Petiveria alliacea* (PA) L. (family Phytolaccaceae) was also used in the community for cancer treatment. However, very few of the traditional healers had used herbs for cancer treatment; most of them had referred their cancer patients to hospitals.

S. scabrida is a familiar herb of tropical Africa present in South South Nigeria, Cameroon, Gabon, the Democratic Republic of the Congo and Angola (Hutchinson, 1954). In the agricultural sector of Nigeria, this shrub has been used as animal feed. The dried root of *S. scabrida* has been used traditionally to treat lower abdominal pains, listlessness, psychosis (Sokomba et., 1986).), sexually transmitted diseases, and bacterial infections (Sokomba et., 1986). Despite the promising use of this plant, there has been no known scientific study conducted to validate its use for the treatment of cancer. Because it grows commonly in the farmlands in the said community and is consumed by the indigenous population for treatment of cancer without any obvious toxicity, it was selected for this study in search of a cancer therapeutic agent that is less expensive and safer.

1.2 Statement of Research Problem

Although many breakthroughs have been made in cancer treatment, it remains a great challenge to both patients and physicians given the failure to achieve a total cure with the current drugs due to the development of resistance, adverse effect, and the imposed significant financial toxicity on the patients (Soefje, 2019). Furthermore, the use of the herb *S. scabrida* and *P. alliacea* in cancer treatment was verbally reported by herbal practitioners in Ugbine community. However, there is no scientific validation and report on the treatment of cancer with SS and the use of PA in prostate and pancreatic cancers.

1.3 Hypotheses of Study

1. Root extracts and isolates of *P. alliacea* and *S. scabrida* exert anticancer activities against cancer cells.
2. Methanol (MeOH) extract is the most active towards PANC-1 cell.
3. SS MeOH extract arrest PANC-1 cell cycle progression.
4. Isolated compounds from SS inhibit PARP1.

1.4 General Objective

To assess the anticancer activity of crude leaf extract of *P. alliacea* and whole root extract of *S. scabrida* together with its major isolated bioactive constituents against colon, prostate, breast, and pancreatic cancer cells *in vitro*.

1.5 Specific Objectives

1. To identify the plants used by Ugbine traditional healers for cancer treatment, through an ethnobotanical study.
2. To evaluate crude extracts of *P. alliacea* and *S. scabrida* for anticancer activity.
3. To identify the most potent extract of *S. scabrida* and the most sensitive cells for further studies.
4. To assess the effect of *S. scabrida* most abundant and potent extract on cell cycle progression.
5. To perform bioactivity-guided isolation of cytotoxic compounds from the roots of *S. scabrida.*
6. To determine the mechanism of actions of the active compounds from *S. scabrida.* using *in silico* molecular docking and molecular dynamics simulation studies.

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