

THE MINING OF NIGERIAN MEDICINAL PLANTS FOR CANCER THERAPY

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OVERVIEW

What is Cancer?

Causes of Cancers and Statistics Cancers

- Advances in the Management and Treatment of Cancers
- The use of Traditional Medicines in the Treatment of Cancers
- Ethnomedical Survey and Anti-cancer Screening of Nigerian Medicinal Plants

Introduction

Tumour is an abnormal growth of cells which form a mass called neoplasm. When the tumor is slow growing and confined to a certain organ it is called benign. Sometimes the tumour can progress into a malignant phenotype while in some situations the cancer cells break away from a tumour mass and spread to other tissues or organs such as the brain and bones through the blood or lymph system. The tumour cells can settle in new places and form new masses. When this happens, the process is called metastasis. This type of neoplasm is called cancer. However certain tumours such as astrocytomas (brain tumors) even when malignant hardly metastasize outside the brain. In contrast breast, prostate and other cancers can metastasize to the brain.

Cancer occurs when cells in a part of the body begin to grow out of control. Normal cells divide and grow in an orderly fashion, but cancer cells do not. They continue to grow and crowd out normal cells. Although there are many kinds of cancers, they all have, in common, this out-of-control growth of cells. Other hallmarks of cancers include; sustained angiogenesis (increased blood vessel supply), high invasive and migratory rates, ability to overcome programmed cell death (apoptosis), limitless proliferative potential, insensitivity to anti-growth signals and self-sufficiency in growth signals (Hanahan and Weinberg, 2000). Different kinds of cancers do not behave in the same manner. For example, lung and breast cancers are very different diseases. Cancers grow at different rates and respond to different treatments. As a result of the heterogeneity of cancers, treatment strategies should be tailored to be patient and cancer-specific.

Causes of Cancers

There are many factors that are implicated in the genesis of cancers and these include genetic and environmental factors. Cancer may result from DNA Mutations which may be caused by (1) radiation and other environmental factors (such as tobacco, alcohol, radon and asbestos), (2) random somatic mutations, (3) inherited germline mutations or genetic predisposition of certain genes such Rb, Ras, p53, APC, CDKN2A, BRCA1, BRCA2 and EGFR. Infectious agents such as viruses may also cause cancer. For example, human papillomavirus (HPV) is involved in cervical cancer and Hepatitis is implicated in liver cancer. Vaccines have been developed for both HPV and Hepatitis which are extremely effective. The bacterium, *Helicobacter pylori* is implicated in the development of stomach cancer. In case of brain tumours,

ionizing radiation, genetic alteration (neurofibromatosis) and certain diets have been shown to predispose the disease. Over the last ten years, cell phones have been suspected to cause brain tumours but large-scale investigations in Europe and the United States failed to provide conclusive evidence linking cell phones to brain tumours in humans. However, in June 2011, the WHO has included cell phones in the category of carcinogens as a result of new evidence that implicated these devices in the genesis of gliomas.

Cancer Incidence and Mortality

Cancer is now the second leading cause of death in the US and Europe, heart disease is number one (See Table1). In the developing countries, cancer is usually considered as a disease of the western world but that is completely wrong. According to the WHO cancer kills more than HIV/AIDS, tuberculosis and malaria combined. The International Agency for Research on Cancer predicts that the annual new cases of cancers are expected to rise from 11 million in 2000 to 16 million in 2020, some 70% of which will be in developing countries.

Table 1 USA Mortality, 2003 (American Cancer Society)

Rank	Diseases	No. of Death	% of All Death
1.	Heart Diseases	685,089	28.0
2.	Cancer	556,902	22.7
3.	Cerebrovascular diseases	157,689	6.4
4.	Chronic lower respiratory diseases	126,382	5.2
5.	Accidents (Unintentional injuries)	109,277	4.5
6.	Diabetes mellitus	74,219	3.0
7.	Influenza and pneumonia	65,163	2.7
8.	Alzheimer disease	63,457	2.6
9.	Nephritis	42,453	1.7
10.	Septicemia	34,064	1.4

In males, there are more cases of prostate cancer diagnosed than any other cancer, while in females' breast cancer is more prevalent than other cancers. Among the cancers, pancreatic cancer is the deadliest with mean survival time of 6 months, followed by glioblastoma multiforme (WHO grade IV malignant brain tumor) which has an average survival period of 9-12 months.

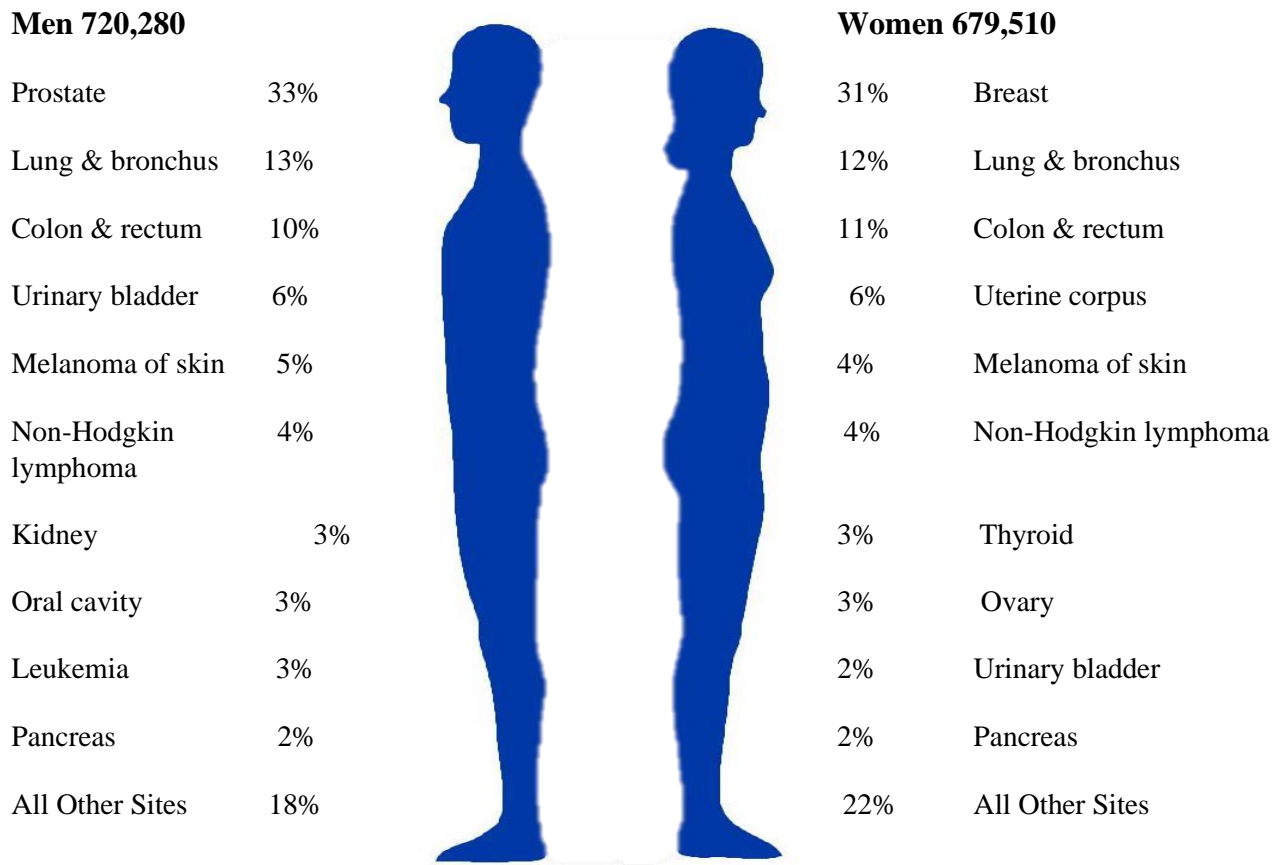


Fig. 1 US Cancer Cases 2006; Source - American Cancer Society

Although the incidences of prostate and breast cancers are highest in men and women, respectively, the rate of cancer death per year is greater with lung cancers than prostate and breast cancers in both genders. This is largely attributed to advancement in early detection techniques for breast and prostate cancers but not lung cancer.

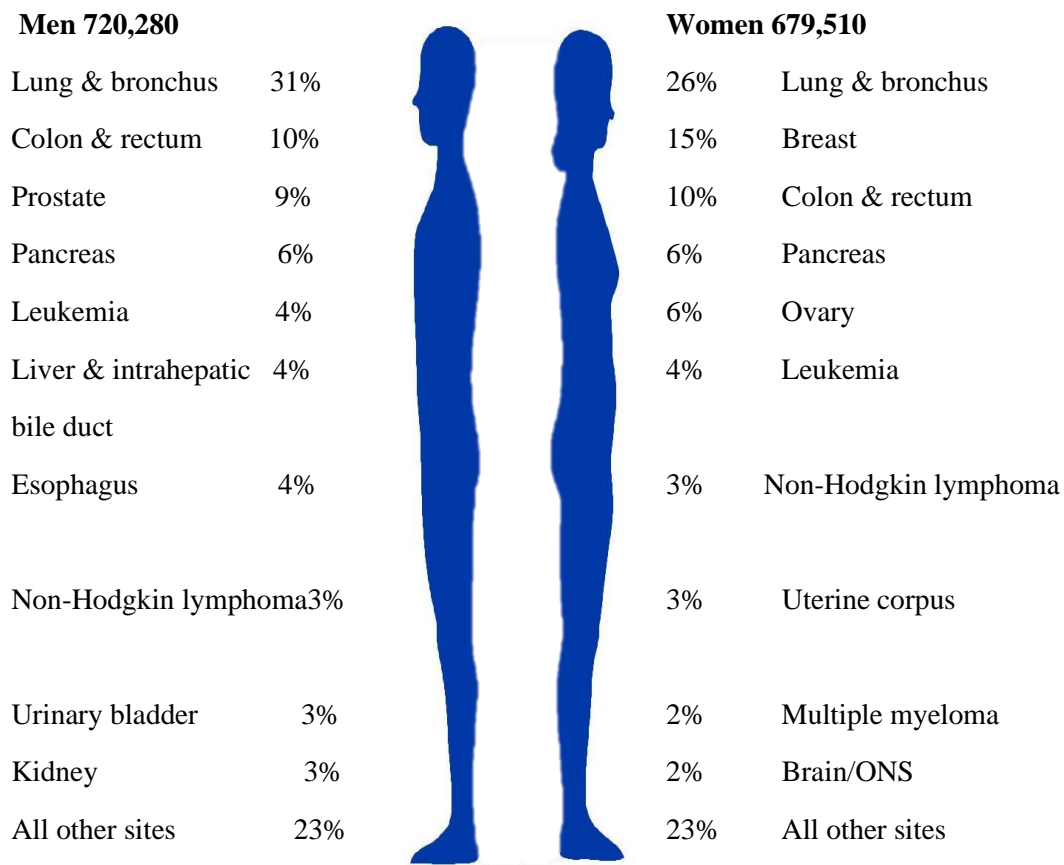


Fig. 1 US Cancer Death: Source - American Cancer Society Website

In a preliminary study conducted at Ahmadu Bello University Teaching Hospital in 2006, we found out that there were more cervical cancers in women than breast cancer, while in men prostate cancer was more prevalent than other cancers in men. The incidence of lung cancers was very low and was below 4% (Mohammed, Abubakar and Hussaini, unpublished data).

Advances in the Management and Treatment of Cancers

Most of significant advances that have been made recently in the management of cancer are in the early detection of the cancers. It is imperative to “catch” the cancers before they become malignant and metastasized. A combination of mammography and manual detection of lumps in breasts have significantly saved the lives of several women from breast cancers. Similarly, analysis of prostate specific antigen (PSA) and rectal examination have helped Urologists and Oncologists to detect prostate cancers before they metastasize outside the prostate gland and become deadly. Colonoscopy has also aided the detection of pre-cancerous polyps before they progress into dangerous colorectal cancers.

Chemotherapy of cancer is the use of chemicals (drugs) to treat or manage the diseases. The treatment modality of choice depends on the stage of the cancer, age, health status and additional personal characteristics. As a result of the high propensity of cancer cells to proliferate, earlier treatment paradigm was geared towards the regulation of the cell cycle. This treatment targets any rapidly dividing cells (normal as well as cancer cells). Chemotherapy is usually recommended for cancer cells that have metastasized because surgical resection would not be useful and whole body radiation has unwanted side effects. Most importantly, drugs that are absorbed into the blood stream can easily be distributed to the organ where the cancer is located. The cell cycle regulators (alkylating agents, vincristine, doxorubicin) act at the levels of

DNA, RNA transcription and protein translation. The problem with such an approach is that normal cells are also affected and the use of cell cycle regulator might lead to unpleasant side effects such as bone marrow suppression and alopecia.

The revolution in molecular biology and the completion of the Human Genome project in 2003 (started in 1990 and a working draft document was released 2000) have provided cancer researchers with newer therapeutic targets. Differential DNA microarray profiling and kinase screening had led to the identification of genes that are either overexpressed or suppressed in cancer cells compared with their normal counterpart cells, which makes these genes unique targets for therapeutic intervention. Epidermal growth factor receptor.

(EGFR), a tyrosine kinase 7-transmembrane receptor, is overexpressed/overamplified (increased gene copy number) by over 40%-60% in number of cancers and tumors including primary glioblastoma multiforme (WHO grade IV brain tumor, GBM), lung and rectal cancers. The Increased expression level or gene copy number of this receptor has been associated with poor prognosis (Herbst 2004). Mutation of EGFR in cancers results in the truncation of the receptor producing a constitutively active EGFR vIII (Kuan, Wikstrand and Bigner 2001). Antibodies (Cetuximab, Zalutumumab) and tyrosine kinase inhibitor (Gefitinib) targeting EGFR have passed clinical trials and are in the clinic for the management of cancers. As a result of overexpression of EGFR, its downstream targets such as Ras, Raf, mitogen activated kinase (MAPK), Akt and mammalian target of rapamycin (mTOR) are putative targets in chemotherapy of cancers (Figure 3). Since two or more pathways are activated following EGFR activation, the recommended approach is the use of a combination therapy to block the pathways involved.

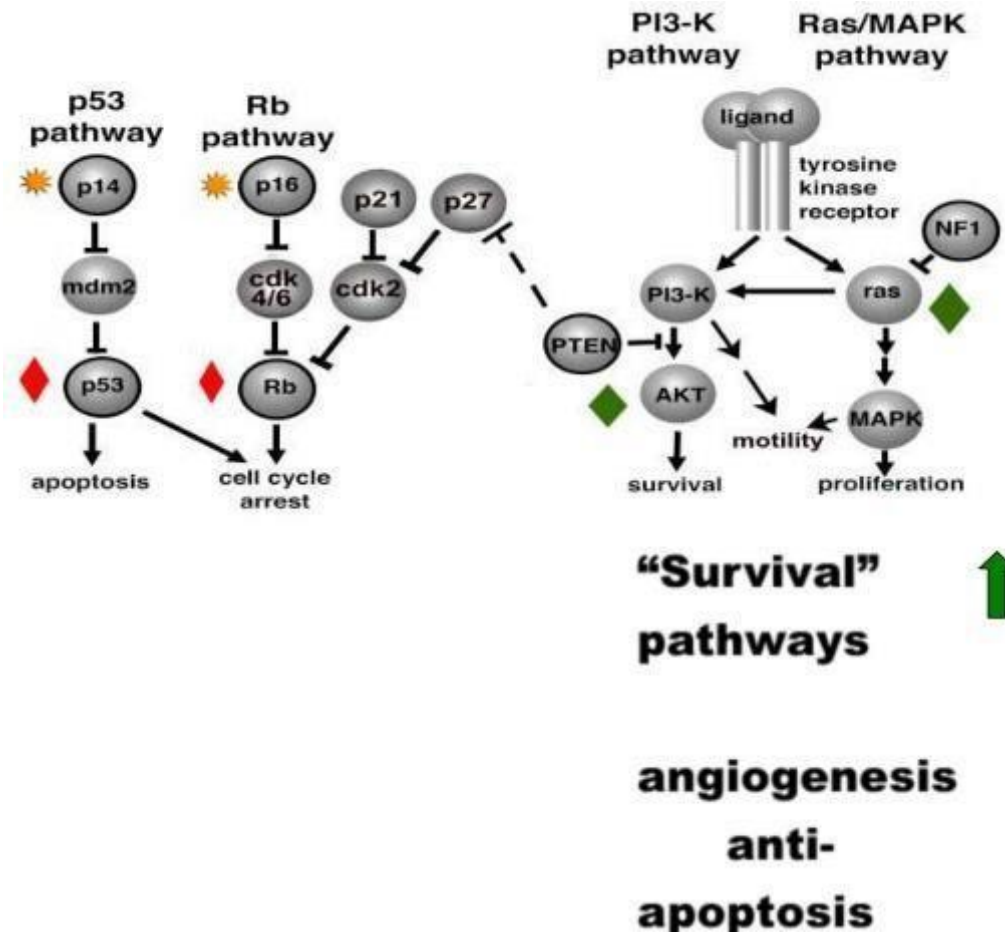


Fig. 3 Signal transduction pathways involved apoptosis, cell cycle arrest and invasive growth

Another EGFR family Her2 is overproduced in about 20% of breast cancers (Isakoff and Baselga, 2011). The HER2-overproducing cancers tend to be more aggressive and are more likely to recur. Trastuzumab, a monoclonal antibody which targets the HER2 protein is used in conjunction with adjuvant chemotherapy to lower the risk of HER2-overproducing breast cancer recurrence by 50% compared with chemotherapy alone. Various researchers have discovered several breast cancer susceptibility genes, including BRCA1, BRCA2, TP53, and PTEN. Mutations in BRCA1 and BRCA2 account for approximately 80-90% of all hereditary breast cancers, and women who carry mutations in these genes have a lifetime risk of breast cancer that is roughly 10 times greater than that of the general population. Strategies targeting some of these genes with chemotherapeutic agents and reversing their mutations would provide new treatment paradigm for breast cancers.

The recent success of cancer chemotherapy involves the use of Gleevec (Imatinib) in the treatment of chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs). The research started in a basic science research laboratory and the product ended up in the clinic. In CML, the Philadelphia chromosome leads to a fusion protein of abl with bcr (breakpoint cluster region) which makes the tyrosine kinase constitutively active and Gleevec decreases bcr-abl activity (Deininger and Druker, 2003). Majority (95%) of CML patients who have abl-bcr fusion respond to Gleevec and the drug has very little effect on normal cells. In addition, Gleevec suppresses platelet-derived growth factor (PDGF) by inhibiting its receptor (PDGF-R β).

The rapidly increasing knowledge of molecular genetics, cell biology and immunology would help cancer researchers to develop more effective and less toxic cancer chemotherapeutic agents. The molecular changes that cause cells to become cancerous would be identified and targeted with drugs. Since genetic alterations vary from patient-to patient, gene signature would be used to provide personalized cancer therapy.

Pharmacogenomic approach is also attracting attention and this would be used to determine a patient's response to chemotherapy because the tumor's genetic characteristics and inherited variation in genes affect a person's ability to absorb, metabolize, and eliminate drugs. This would allow prediction of tumor response to individual chemotherapy drugs or class of drugs. This strategy should also aid in the design of more effective and less toxic chemotherapeutic agents.

The use of Traditional Medicines in the Treatment of Cancers

The typical African health sector in the rural areas consists of traditional healers and birth attendants, who are the de facto providers of primary health care. Healers provide client centered and personalized health care that is culturally appropriate, holistic and tailored to meet the needs and expectations of the patients (Iwu, 1994). There is also a general belief that the remedies used in traditional medicine are safe and more readily acceptable by the body. This is far from the truth because of the numerous reported cases of toxic and lethal effects of herbal medications.

One of the major challenges facing traditional headers is the lack of knowledge in proper diagnosis of diseases such as cancer. Some believe that cancers occur as a result of contact of patients with evil spirits in the forest or bush and thus the general term “daji” (bush in Hausa) to describe cancer. Interestingly, some of Traditional Medicine Practitioners (TMPs) have some basic knowledge of specific cancers, for example they describe leukemia and believe that it is inherited. However, they believe that leukemia is more frequent in families with a history of sickle cell anemia. The latter may have some medical and scientific merits.

The use of plant-derived medications dates back to pre-historic periods. Modern plant based drugs were discovered as early as late 17th century and they include aspirin (analgesic), morphine (narcotic analgesic), digitalis (antiarrhythmic agent), and quinine (anti-malarial). Some plant alkaloids such as vinblastine and vincristine (Vinc Alkaloid) are used to manage cancers. Recently, Paclitaxel (Taxol) was isolated from Yew tree and is now used for the management of melanoma, ovarian, lung and breast cancers.

Plant Name	Family	Local Name	Part Used	Cancer- type
Cissus ibuensis Hook	Ampelidaceae	Daddori	Leaves	Skin cancer
Annona senegalensis Pers.	Annonaceae	Gwandar daji	Stem bark/leaves	Skin cancer/leukemia
Aristolochia albida Dulchartre	Aristolochiaceae	Duman dutse	Rhizomes	Many forms of cancers
Leptadenia hastata Pers	Asclepiadaceae	Yaadiya	Aerial parts	Cancers in general
Maytenus senegalensis Lam.	Celastraceae	Mangaladi	Leaves	Cancers in general
Ximenia Americana Linn.	Olacaceae	Tsaada	Fruits	Many forms of cancers

In 2006, we carried out an ethnomedical survey of medicinal plants used in the treatment of cancers among the Hausa-Fulani tribes in Kaduna State (Abubakar, Adamu and Hussaini, 2007). We found a number of plants that are used in the treatment of “daji” (cancer) and these are presented in Table 2.

In 2012, we discovered another plant, *Senna siamea* (family = fabaceae) that showed antitumor activity. An undergraduate student (Nasiru) of the University of Maiduguri under the supervision of Pharmacist Yabalu Abacha (Department of Pharmacognosy) screened the *Senna* parts for cytotoxicity using shrimps and later we extended the study to human brain tumours. *Senna* root extract was incubated with malignant brain tumor (glioblastoma multiforme; GBM) for 48 hours. GBM cells were washed three times and fixed with 1% crystal violet. The cells were then photographed under microscope. The ethanol extracts (50 – 250 g/mL) of *senna siamea* roots and leaves were screened for anti-tumor activity against GBM cells. The root extract was effective in killing the tumor cells at a low dose of 50 g/mL while the leaf extract was not effective at even 250 g/ml. Figure 4 shows untreated (control) and extract-treated (250 g/mL) GBM cells. The root extract killed over 70% of the tumor cells within 48 hours.

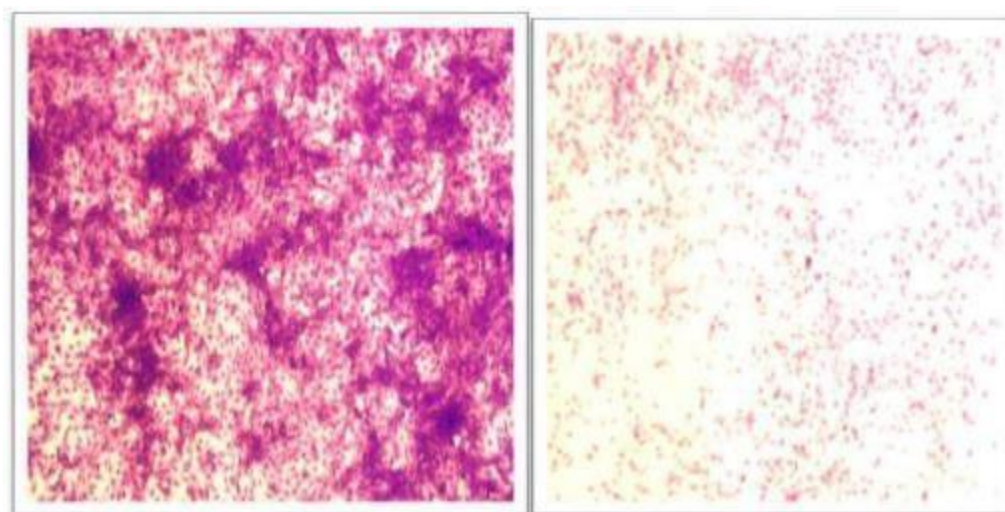


Fig. 4 - Anticancer Activity of *Senna siamea*

In a preliminary study, we tested *N. sativa* seed (Black Caraway) for anticancer activity. The plant is extensively used in the Middle East, North Africa and Borno State for the treatment of a variety of ailments, including epilepsy, inflammation, asthma and others. The ethanol (BC-ETOH) and hexane (BC-H4) fractions of the seeds of *N. sativa* killed brain tumours (Figure 5). The results were generated by counting the number of tumour or cancer cells before and after treatment with the ethanol extract of the plant. The anticancer activity was associated with the oil fraction of the seed which also activated caspases-3 and 9 (death-mediating genes) and down-regulated insulin growth factor receptor-1 (survival factor). These factors are involved in tumorigenesis.

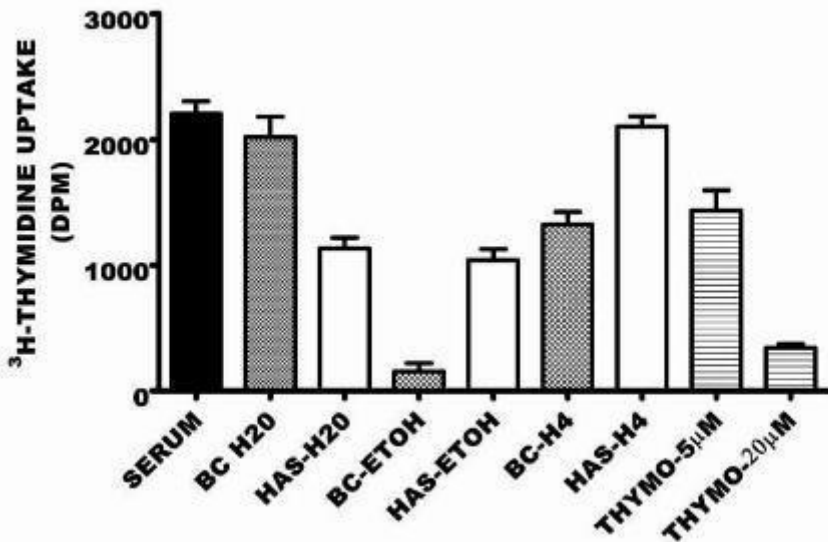


Fig. 5 Anti-proliferative activity of different fractions of Black Caraway and thymoquinone on glioblastoma cells.

Using Mass Spectrometry and nuclear magnetic resonance (NMR), we identified the active compound as thymoquinone. The IC₅₀ values for the oil fraction of black caraway and thymoquinone were determined to be 250 g/ml and 6.0 M (n=5). □ □

N. sativa oil and thymoquinone-induced apoptosis in GBM cells - To determine the mechanism(s) of *N. sativa* seed oil-induced GBM death, we performed propidium iodide (PI)/Hoescht staining to assess the number of dead/apoptotic cells. The Hoescht dye has the property of freely passing through the plasma membrane and readily enters cell with intact membranes as well as cells with damaged membrane and stains blue, whereas PI (a highly polar dye) is impermeable to cells with preserved membranes and stains red. In Fig. 6, it is clear that *N. sativa* (250 g/ml) and thymoquinone (10 M) treatment significantly killed more malignant brain tumours compared with control. We had also confirmed the efficacy of both the oil and thymoquinone in our xenograft animal model. □

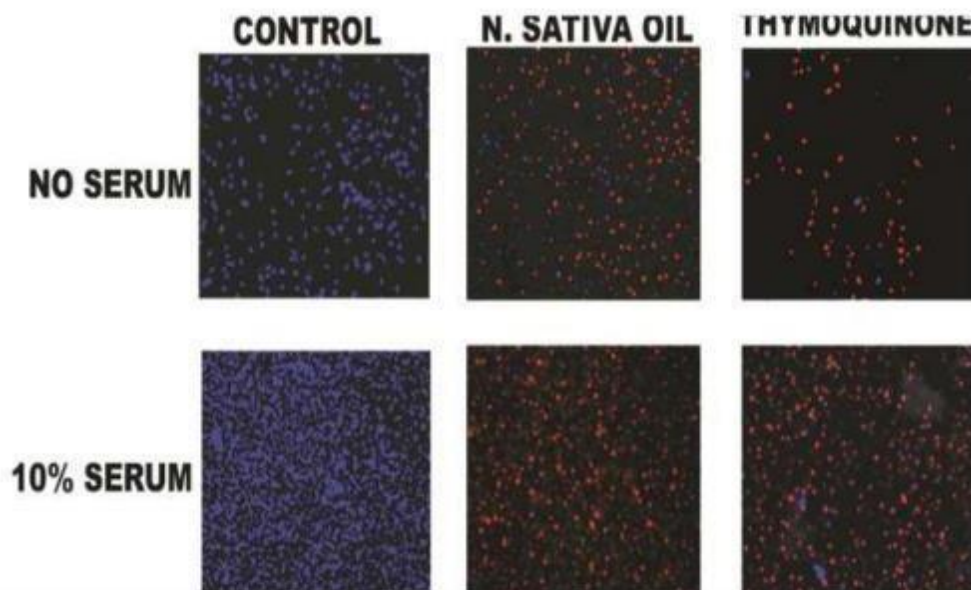


Fig 6. Propidium Iodide/Hoescht Staining of Astrocytoma Cells

Ethnomedical Survey and Anti-cancer Screening of Nigerian Medicinal Plants

Cancer Prevalence - Cancer is the second leading cause of deaths in many countries and there is no cure for most of the diseases. In Africa, traditional medicine practitioners (TMP) claim to have effective treatments for what they diagnose as “cancers”. The cancer research project at the University of Maiduguri used scientific techniques to validate the rationale for the folkloric use of herbal medications by TMP. To find out the types of cancers diagnosed in the North East geopolitical zone of Nigeria, we collected data from patients who attended the University of Maiduguri Teaching Hospital for the treatment of cancers for 5 years (2006 – 2011). Prostate and skin cancers were more common in men and breast and cervical cancers were more prevalent among women (Table 3). Based on this finding, we are now focusing our studies on these cancers and brain tumours. The latter is the second deadliest tumour/cancer. Three Co-PIs (Dr. Bala Audu, Dr. Babayo Usman and Dr. Ahmed Mayun) will continue to work on this aspect of the project and establish a Cancer Registry for the North Eastern region of Nigeria.

Table 3 - Leading cancer-types registered at the University of Maiduguri Teaching Hospital 2006-2011 (5 Years)

SITE	NUMBER	FREQUENCY
BREAST	357	17.0
CERVIX	318	15.1
PROSTATE	232	10.9
SKIN	224	10.6
GIT	208	9.6
ENT	179	8.5
OVARY	91	4.1
BLADDER	64	3.0
STOMACH	41	1.9
ENDOMETRIUM	33	1.6
TOTAL	2104	100.0

In the second part of the study, ethnomedical survey of plants used in the treatment of cancers (daji) in the North-East geopolitical zone of Nigeria was carried out. We identified 54 plants that are used in the folkloric treatment of cancers. The botanical and local names of some of the plants are presented in Table 4.

We defatted the plant parts that are used in folkloric medicine with petroleum ether and further extracted the residue with ethanol. The dried extracts were screened for anticancer activities against well-characterized brain tumour (A171, U87 and U1242) and breast cancer (231) cell lines. The extracts were coded ETF1-54 and all screenings were carried out blind. In the initial screen three samples (ETF3, 6 and 20) out of ten extracts were found to be highly effective in killing brain tumour and breast cancer cell lines. Subsequently, we screened 44 extracts and established robust anticancer activities of 8 plants.

Table 4. Some of the Plants used in the treatment of cancers by TMPs.

S/N	Botanical name	Family name	Hausa name	Uses	Parts used
1	<i>Boswellia dalzielli</i>	Burseraceae	Arrarabi	Cancer	Bark
2	<i>Commiphora</i>	Africana Burseraceae	Dashi	Cancer	Bark, leaves, roots
3	<i>Cadaba farinose</i>	Capparidaceae	Bagayi	Cancer	Leaves, root, bark
4	<i>Commiphora pedunculata</i>	Burseraceae	Daddasa/ namijin dashi	Cancer	Leaves, root, bark
5	<i>Maerua angolensis</i>	Capparidaceae	Mandewa	Cancer	Leaves, stalk, bark
6	<i>Piliostigma reticulatum</i>	Caesalpiniaceae	Kargo	Cancer	Bark, leaves, root
7	<i>Euphorbia hirta</i>	Euphorbiaceae	Nonon kurciya	Cancer	Leaves, whole plant
8	<i>Ziziphus abyssinica</i>	Rhamnaceae	Magaryan kura	Cancer	Bark, leaves, root
9	<i>Acacia albida</i>	Mimosaceae	Gawo	Cancer	Bark, leaves, root
10	<i>Guiera senegalensis</i>	Combretaceae	Sabara	Cancer	Leaves. root
11	Acacia Senegal	Mimisaceae	Dakwara	Cancer	Leaves, bark, root
12	<i>Terminalia avecenniodes</i>	Combretaceae	Baushe	Cancer	Bark, leaves, root

13	Ximenia ameerica	Olacaceae	Tsada	Cancer	Leaves and bark, root
14	Capparis tomentosus	Capparidaceae	Kabdodo	Cancer	Leaves, root, stalk
15	Albizzia chevalier	Mimisaceae	Katsari	Cancer	Leaves, bark, root
16	Sterospermum kuthianum	Bigniniaceae	Samsami	Cancer	Bark, root
17	Acacia ataxacantha	Mimisaceae	Duhuwa	Cancer	Leaves, root
18	Vitellaria paradoxa	Saotaceae, Sapotacea	Kadanya	Cancer	Bark, root, leaves, seeds
19	Sansevieria spp	Moda/kabar	Giwa	Cancer	Root, leaves
20	Opuntia inermis	Cactaceae	Takalmin binta	Cancer	Whole plant
21	Amaranthus spinosus	Amaranthaceae	Zaaki banza mai kaya	Cancer	Whole plant
22	Leptadermia hastate	Asclepiadaceae	Yadiya	Cancer	Leaves, stalk, root, whole plant
23	Asparagus Africana	Liliaceae	Adamu adawa	Cancer	Bark, leaves, root
24	Acacia nilotica	Mimosaceae	Gabaruwa /kasa	Cancer	Leaves
25	Ziziphus spina chriti	Rhamnaceae	Kurna	Cancer	Leaves, bark, root
26	Annona senegalensis	Annonaceae	Gwandan daji	Cancer	Bark, stalk, leaves, root

27	<i>Tamarandis indica</i>	Caesalpiniaceae	Tsamiya	Cancer	Bark, dry fallen bark, leaves, root
28	<i>Cassia singuena</i>	Caesalpiniaceae	Rumfu	Cancer	Leaves and stem, root
29	<i>Ampelocissus grantii</i>	Vitaceae	Rogon jeji	Cancer	Root, leaves, stalk
30	<i>Cassia siberiana</i>	Caesalpiniaceae	Marga/ dankila	Cancer	Roots, leaves, bark
31	<i>Senna siamea</i>	Caesalpiniaceae	Flawan turawa	Cancer	Bark, leaves

Three of the plants showed impressive anti-cancer activities against both breast cancer and brain tumour (Figures 6 and 7). The order of relative potency is EFT20 < ETF6 < E T F 3. The ETF20 killed both breast cancer and brain tumour cells at a very low concentration of 12.5 µg/mL. Later, we screened the remaining plant extracts and presented in Table 5. Three pluses (+++) means the extract killed over 80% of the cancer cells at 250 g/m l while two pluses (++) represents over 80% death with a higher concentration of 500g/ml.

Figure 6. Effect of Ethanol Extracts on Brain Tumour Cell Viability

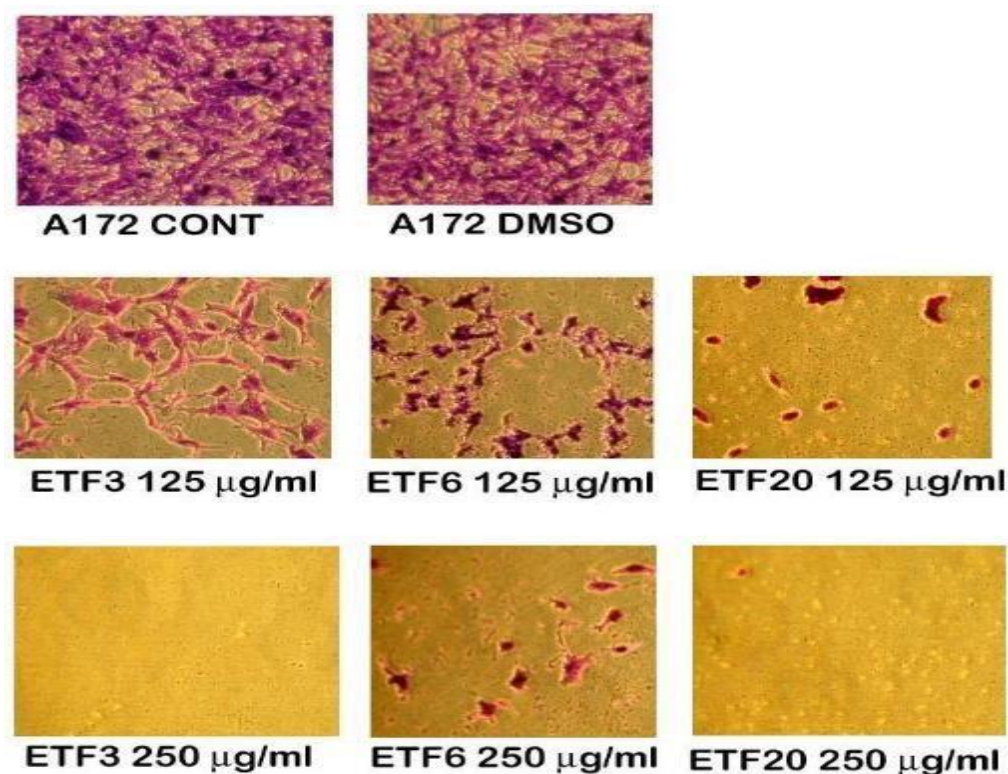
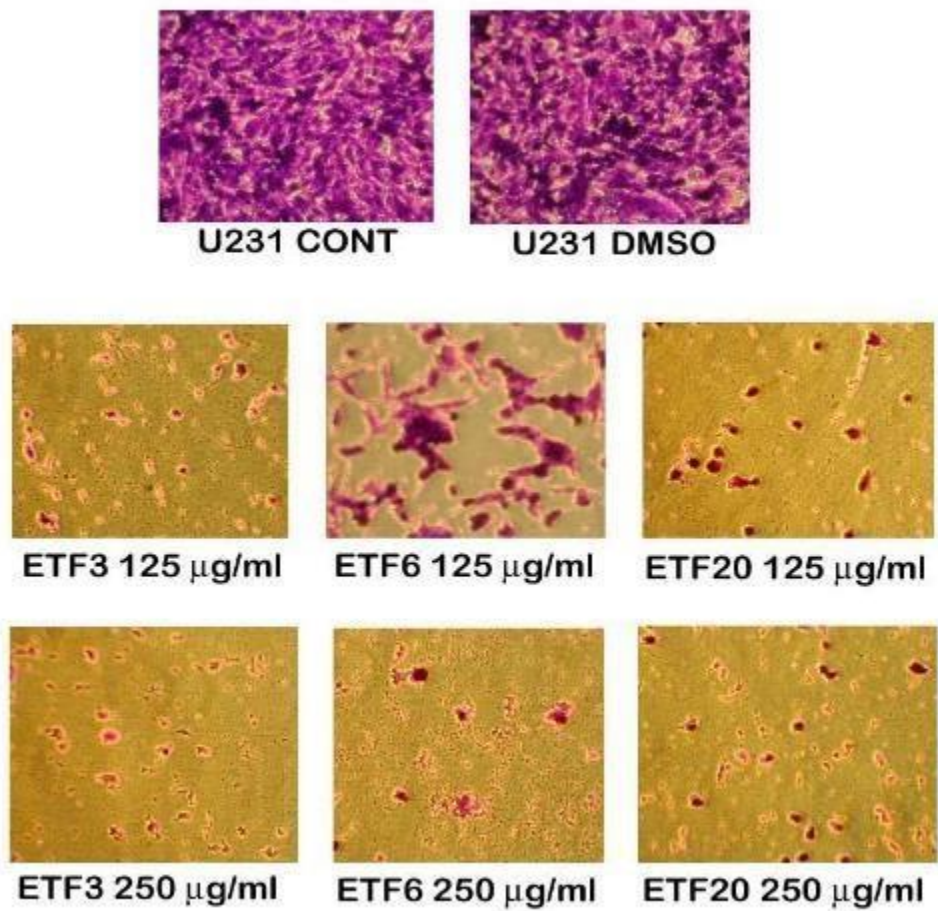


Figure 7. Effect of Ethanol Extracts on Breast Cancer Cell Viability.



EXTRACT	BRAIN TUMOURS	BREAST CANCERS
E TF1	+	-
E TF2	-	+
E TF3	+++	+++
E TF4	-	-
E TF5	-	-
E TF6	+++	++
E TF7	-	-
E TF8	-	-
E TF10 (E A M A D 1)	-	-
E TF20 (E A M A D 2)	+++	+++
PLANT EXTRACT	ACTIVITY AGAINST BRAIN TUMOUR	ACTIVITY AGAINST BREAST CANCERS
E TF9	+++	++
E TF10	+	+
E TF11	++	++
E TF12	+++	+++
E TF13	-	-
E TF14	-	-
E TF15	-	-
E TF16	-	-
E TF17	-	+
E TF18	+	-
E TF19	+++	++

PLANT EXTRACT	ACTIVITY AGAINST BRAIN TUMOUR	ACTIVITY AGAINST BREAST CANCERS
E TF20	-	-
E TF21	-	+
E TF22	-	-
E TF23	+	+
E TF24	-	-
E TF25	-	-
E TF26	-	-
E TF27	-	-
E TF28	-	-
Z-7	+++	+
Z-9	++	-
J A -B	+++	+++
J A -C	-	++
J A -I	++	++

Current and Future Plans for Cancer Research at the University of Maiduguri

Traditional herbal medications are used extensively for the treatment of a variety of diseases including cancers in Nigeria. We will continue to use this untapped and rich source of herbal plants in combination with modern tools to provide scientific rationale for the folkloric use of these medications. The first task is to establish a robust database of all possible plants used in the former North Eastern State of Nigeria. We have increased our database to approximately 200 plants. The second phase of the project is to screen these plants for their anticancer properties using established cancer cell lines, patient cancer specimens, cancer stem cells and animal models of cancers, which will be followed by identification of active principles in the plants using mass spectrometry and NMR analyses.

The anticancer screening was carried out at the University of Virginia, Charlottesville Virginia, USA. We have now established a world-class Tissue Culture Facility for growing well-characterized cancer cell lines and primary cancers from patients. The setting up of a standard Tissue Culture Facility, dedicated laboratory for cancer research and the use of molecular techniques to investigate the underlying mechanisms for anticancer properties of Nigerian herbal plants will place the University of Maiduguri as a Centre of Excellence for cancer research and the best Cancer Research Institution in Africa.

Challenges for Cancer Research

- (1) Insecurity
- (2) Inadequate Funding
- (3) Unreliable power supply
- (4) Lack of Institutional and Government Support

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