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## Review

# A review of twenty ethnobotanicals used in the management of breast cancer in Abeokuta, Ogun State, Nigeria

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Ethnobotanical investigation revealed the use of *Alafia barteri* Oliv., *Allium ascalonicum* L., *Alstonia congensis* Engl., *Anthocleista djalonensis* A. Chev., *Calliandra portoricensis* (Jacq.) Benth., *Capsicum frutescens* L., *Clausena anisata* (Willd.) Hook f. ex Benth., *Erythrophleum suaveolens* (Guill. & Perr.) Brenan, *Grewia flavescens* Juss., *Khaya ivorensis* A. Chev., *Kigelia africana* (Lam.) Benth., *Lophira alata* Banks ex C.F. Gaertn., *Macaranga barteri* Mull. Arg., *Olex subscorpioidea* Oliv., *Plumbago zeylanica* L., *Tephrosia vogelli* L., *Tetracera alnifolia* Willd., *Tetrapleura tetraptera* (Schum. & Thonn.) Taub., *Triclisia subcordata* Oliv., and *Xylopiya aethiopica* (Dunal.) A. Rich. in the management of breast cancer in Ogun State, Nigeria. The prevalence of breast cancer in Nigeria was 15.3 per 100,000 in 1976 and 33.6 per 100,000 in 1992. Breast cancer is the leading malignancy in the South Western Nigeria; it is second to cancer of the cervix in the north-west. In north-central, 22.41% of new cancer was registered for breast cancer in five years and accounted for 35.41% of all cancers in women. The limitations of orthodox drugs such as cost, accessibility, effectiveness, and side effects necessitate the search for cheap, safe and effective phytomedicine in cancer management. Thus, this paper reviewed twenty plants used traditionally for the management of breast cancer; this was with a view to presenting them for future research activities and scientific validation of their potency in cancer regimen.

**Key words:** Ethnobotanicals, breast cancer, traditional recipes, Ogun State, Nigeria.

## INTRODUCTION

Cancer is one of the most dreaded diseases threatening the health conditions of mankind. It is among the killer diseases in Nigeria, and a name associated with a group of diseases in which the body cells divide, multiply and spread uncontrollably (Bolarin, 2009). They may also be regarded as a large family of diseases which show

features suggestive of malignancy. They form a subset of neoplasm. The disease causes about 13% of all world death (Soladoye et al., 2010). Worldwide, approximately 18% of cancer deaths are related to infections, such as hepatitis B, hepatitis C, and human papilloma virus. This proportion varies in different regions of the world from a

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high of 25% in Africa to less than 10% in the developed world. Deaths from cancer worldwide are projected to continue rising with an estimated 12 million deaths in 2030; case reports from 2007 indicated that about 7.6 million people died from cancer in the world (NCI, 1999). In 2012, about 14.1 million new cases of cancer occurred globally. It caused about 8.2 million deaths or 14.6% of all human deaths (Fox et al., 2005).

## DESCRIPTION OF CANCER

Although, cancer is a general term for uncontrolled and abnormal growth of cells, most types form a lump or mass called tumour. Persistence of growth is a salient feature of tumour cells, and this distinguishes them from other normal/healthy body cells. Not all tumours are cancer; any tumour that is not a cancer is said to be benign or less technically, simple tumour. If the process of tumour formation endures, it leads to death of the individual (Dardi et al., 2012). Viruses are the usual infectious agents that cause cancer, but bacteria and parasites may also have an effect. Malignant tumours are generally cancers (Bolarin, 2009) and are caused by a breakdown of genetic material of resulting cells and these may be due to the effect of physical carcinogenic agents, such as tobacco smoke, ionizing radiation, chemicals, or infectious agents (Soladoye et al., 2010) which damage the DNA of a critical gene in a cell; this DNA damage invokes mutations leading to irregularities in the gene function (Bolarin, 2009). Cells from a tumour can break away and be transported to other parts of the body, a process described as metastasis, where they continue to grow. Benign tumours do not grow and spread the way cancer does. They arise from one site, grow by expansion, local, only harmful through size and pressure, and do not recur after surgical removal, whereas malignant tumours or cancers grow by invasion and infiltration, become fixed to surrounding structures, develop secondary growths or metastasize and tend to recur after surgical treatment. In many cases, however, cancer may present as "hard swellings", abscesses, calluses, corns, warts, polyps, or tumours, and are thus classified as undefined (Mouli et al., 2009). Many cancers can be prevented by not smoking, eating more vegetables, fruits and whole grains, eating less meat and refined carbohydrates, maintaining a healthy weight, exercising, minimizing sunlight exposure, and being vaccinated against certain infectious diseases. Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year (NCI, 1999).

## TYPES OF CANCER

Over 200 types of cancer have been reported. Most cancers are classified according to symptoms presented

or cellular morphology, which resemble to some extent the tissue from which the cancer originates. Classification may also follow the categories reported by NCI (1999). Broadly, this may include carcinoma, sarcoma, lymphoma, myeloma, and central nervous system cancers. Other groups are leukaemia, germ cell tumour, melanoma, and gliomas. However, histological classification or grouping of cancers depends on identifying the basic cell type present and on the tissue of origin, not according to tissue in which they may have spread.

## CLINICAL MANIFESTATIONS

Almost all parts of the body are susceptible to cancer infection; however, some areas are more vulnerable than the others. Although, cancer is a non-communicable disease, the incidence and severity has greatly increased and common among older individuals. Cancer is not restricted to humans; animals and other living organisms may also be afflicted. Cancer may affect people at all stages, even foetus, but the risk for most cancer types increases with age. General presentation of cancer symptoms are lump or swelling in the breast, difficulty in swallowing, indigestion, bleeding, persistent cough, urinary difficulty, and unusual or irregular discharge. Other signs and symptoms may include a new lump, abnormal bleeding, a prolonged cough, unexplained weight loss, and a change in bowel movements (Saunders and Jassal, 2009). However, while these symptoms may indicate cancer they may also occur due to other issues. The most common cancers in men, women and children in the world over are as follows: Men (prostate, lung, and colorectal); Women (breast, lung, and colorectal); Children (leukaemia, brain tumours, and lymphoma).

## CAUSES OF CANCER

The growth of the cancer cells is purposeless, parasitic and flourishes at the expense of the human body (Olapade et al., 2012). The factors which cause cancer development are vaguely known. According to Bolarin (2009), causes of cancer in Africa may include occupation, climate, habits, rural area habitation, food, drink, virus, stress, drugs, and trauma. Age, sex, race, and local environment are other probable factors. On the whole, common environmental factors that contribute to cancer death include tobacco (25 to 30%), diet and obesity (30 to 35%), infections (15 to 20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants (Fox et al., 2005). Exposure to particular substances has been linked to specific types of cancer; these substances are called carcinogens.

## BREAST CANCER

Breast cancer is a malignant tumour arising from the cells of the breast or breast tissue and mainly occurs in women, although men can also develop the disease. Breast cancer can start in the ducts or lobules of the breast. When the cancer cells stay in the ducts and lobules of the breast, this is called non-invasive breast cancer. If the cancer cells spread into the surrounding tissue, this is called invasive breast cancer. However, there are several types of abnormal growth of cells in the breast tissue most of which are benign and they include fibroadenoma, breast cysts, mammary dysplasia, cystosarcoma phylloides, duct ectasia, traumatic fat necrosis and sclerosing adenosis (Okobia, 2000). Others, according to Stoppler (2012), are invasive lobular carcinoma, mucinous carcinoma, medullary carcinoma, triple-negative breast cancers, Paget's disease of the nipple, etc. Breast cancer may present as painless swelling, blood-stained nipple, retraction of the nipple, discharge, lymphoedema, eczema or dermatitis of the areola and metastasis.

### Prevalence of breast cancer in Nigeria

In Nigeria, breast cancer is the commonest among women and the incidence, as submitted by Okobia (2000), seems to be on the increase. The incidence in Nigeria is 15.3 per 100,000 in 1976 and 33.6 per 100,000 in 1992 (Ihekweba, 1992). Reports from studies in some parts of Africa have confirmed breast cancer incidence, severity and continued rise (Ngendahayo and Parkin, 1986; Menye et al., 1992). In the year 2000, an estimated 1.05 million cases were recorded; hence, breast cancer was regarded as the most common cancer in women (Parkin et al., 1999). Cancer incidence and severity varied for the six geopolitical zones in Nigeria. Afolayan (2008) reported breast cancer as the leading malignancy in the southwestern part, whereas Ogunbiyi et al. (2010) submitted that it is second to cancer of the cervix in the northwest. In north central, 22.41% of new cancer was registered for breast cancer in five years and accounted for 35.41% of all cancers in women (Afolayan et al., 2012). Reports from Lagos State Ministry of Health documented 13% new cases and in women under 30 year. Breast cancer had a prevalence of 11.2% between 1960 and 1980, and 25.7% between 1981 and 1995 (Adetifa and Ojikutu, 2009).

### Treatment options

The main purpose of treatment is to eliminate the cancer. The treatment procedures depend on the type of cancer and the stage. However, majority of cancer patients report to the hospital late when the disease might have

advanced thereby presenting tumours that are fungated, foul smelling and bleeding (Gadhvi, 2002). Treatment modalities are always changing and developing. Options include surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, and traditional herbal medicine. In Nigeria, most cancer patients are usually treated in hospitals: federal, state and specialist (teaching) hospitals, where facilities are available for effective care. Some private hospitals are also well equipped with modern facilities to handle cancer cases, whereas some organizations provide specialized training in cancer research to college students (Cancer Research Institute, Hawaii, USA).

## REPORTS ON PLANT-DERIVED ANTICANCER AGENTS

Anticancer agents can broadly be divided into three, namely, alkylating agents, antimetabolites, and natural products (Dardi et al., 2012). These agents have been used in the management of both benign and malignant tumours. In cancer chemotherapy, an active ingredient extracted from *Podophyllum peltatum* L. has been used by Native Americans in the treatment of cancer (Imbert, 1998). However, the limitations of orthodox drugs, such as cost, accessibility, effectiveness, and side effects necessitate the search for cheap, safe and effective phytomedicine in cancer management. The cytoprotective properties of many herbs, fruits and spice plants have been reported by Konczak et al. (2009), as these natural medicines are a rich source of phenolic compounds, vitamins C and E. *In vitro* and *in vivo* studies of the seeds of *Acacia victoriae* (Benth.) from Native Australia confirmed anticancer, anti-inflammatory and antioxidant activities of novel compounds derived from the seeds (Hanausek et al., 2001; Haridas et al., 2009). Studies conducted independently using mouse models and *in vitro* assays by Konczak et al. (2009), Symonds et al. (2009), and Symonds and Fenech (2009) found the fruit extract of *Podocarpus elatus* R. Br. ex Endl. to exhibit significant antioxidant and pro-apoptotic anticancer activity; it also reduced the proliferation and altered the morphology of colon cancer cells and prevented the development of obesity. Anticancer activity of Egyptian medicinal plants was evaluated *in vitro* against Acute Myeloid Leukaemia (AML) and Acute Lymphoma Leukaemia (ALL); the *in vivo* assay against Ehrlich Ascites Carcinoma Cells (EACC) showed significant antioxidant activity when 2, 2' diphenyl picryl hydrazyl (DPPH) radical method was used (Nassr-Allah et al., 2009). Several other studies have confirmed the anticancer potential of herbal medicine *in vitro* and/or *in vivo* (El-Shemy et al., 2007; Hu et al., 2002). Aqueous extracts from leaves of *Salix* species prevented proliferation of AML, ALL and EACC (El-Shemy et al., 2007). Mushrooms have also been identified as



**Table 1.** Main natural products used as tumour inhibitors and their plant sources (Dardi et al., 2012).

Class	Compound	Plant source	Family
Monoterpene	Allamandin	<i>Allamanda cathartica</i> L.	Apocynaceae
	4-Ipomeanol	<i>Ipomoea batatas</i> (L.) Lam.	Convolvulaceae
Diterpene	Jatrophone	<i>Jatropha gossypifolia</i> L.	Euphorbiaceae
	Taxoldione	<i>Taxodium distichum</i> (L.) Rich.	Cupressaceae
	Taxol	<i>Taxus brevifolia</i> Nutt.	Taxaceae
Lignan	$\alpha$ - and $\beta$ -peltatin	<i>Podophyllum peltatum</i> L.	Berberidaceae
	Podophyllotoxin	<i>Podophyllum hexandrum</i> Royle	Berberidaceae
		<i>Podophyllum peltatum</i> L.	Berberidaceae
Isoquinoline	Emetine	<i>Cephaelis cuminata</i>	Rubiaceae
Bis-indole	Leurosine	<i>Catharanthus lanceus</i> (Bojer ex A. DC.) Pichon	Apocynaceae
	Vinblastine	<i>Catharanthus roseus</i> (L.) G. Don	Apocynaceae
	Vincristine	<i>Catharanthus roseus</i> (L.) G. Don	Apocynaceae
Non-heterocyclic peptide	Colchicine	<i>Colchicum speciosum</i> Steven	Colchicaceae

viable anticancer agents. The ethanol extract of *Ganoderma lucidum* induced apoptosis in MCF-7 human breast cancer cells. Luffin, a chemical constituent of *Luffa aegyptiaca* Mill. was found to be cytotoxic to the human metastatic melanoma with greater efficacy in Ehrlich cells (Poma et al., 1998). The main natural sources of tumour inhibiting agents are presented in Table 1.

Also, worthy of note are the first generation anticancer drugs from plant sources (Table 2). Many of these anticancer agents are in clinical use all over the world; notable ones are taxol, vinblastine, vincristine, camptothecin derivatives, topotecan and irinotecan, and etoposide. Vincristine has proven to be clinically important than vinblastine, and is used in the treatment of infant leukemia; others that may enter preclinical and clinical trials include flavopiridol, silvestrol, roscovitine, combretastatin (Shoeb, 2006). The NCI started long ago the development of anticancer formulations on clinical trials (Cragg and Newmann, 2005). Shoeb (2005, 2006) isolated two new alkaloids from *Centaurea schischkinii* L. and *Centaurea Montana* L.; these compounds exhibited significant cytotoxic effects against human colon cancer cell lines. Combretastatin isolated from *Combretum caffrum* Kuntze was active against colon, lung, and leukemia cancers (Ohsumi et al., 1998). Although, most tumours are now resistant to anti-neoplastic drugs, research is on-going to identify and develop more effective agents against cancer. Oloyede et al. (2012) reported *Allium ascalonicum* L. water and chloroform fractions exhibited the strongest cytotoxicity on VERO cell lines, whereas water fractions of *Securidaca longepedunculata* Fresen. were most potent in the CEF

cells. Metabolites and mechanism of action of some anticancer drugs from plant sources is presented in Table 2.

Most anticancer agents exhibit their activity by the inhibition of nucleic acid synthesis. This inhibition is manifested in the mitotic division of cells; the drugs bind to proteins in the mitotic spindles preventing polymerization and the assemblage into microtubules (Dardi et al., 2012). The inhibitory activity of other anticancer agents differs markedly; some microtubules are stabilized against depolarization. Flavopiridol (a semi-synthetic flavone) works by inhibiting cell cycle progression at G1 or G2 phase and interfering with the phosphorylation activity of cyclin-independent kinases (Nirmala et al., 2011). Crude extracts of most plants have been screened for anti-proliferation against several cancer cell lines; results obtained from these screens have necessitated the need for more through-put screening methods. In more recent research, the activity of semi-synthetic products against cancer cell lines has been explored. For example, resins from the root of *Podophyllum hexandrum* Royle and *Podophyllum peltatum* L. are not used systematically; the semi-synthetic derivatives (podophyllotoxin) have given good results in clinical trials.

Mans et al. (2005) reported that, about 1,500 extracts have been screened from 500 species that are now in various stages of clinical research. Luteolin (a compound found in virtually all plant families (Lopez-Lazaro, 2009) has been shown to have broad-spectrum pharmacological action including cancer chemopreventive and chemotherapeutic activity. Various

**Table 2.** Metabolite and mechanism of action of some anticancer drugs from plant sources.

Drug/Metabolite	Plant source	Family	Mechanism of action	References
Vinblastine, Vincristine, Vinorelbine, Ajmalacine	<i>Catharanthus roseus</i> (L.) G. Don	Apocynaceae	Inhibition of tubulin polymerization	Kumar et al. (1997); Schwartzmann et al. (2001)
Taxol, Docetaxel Paclitaxel	<i>Taxus baccata</i> L. <i>Taxus brevifolia</i> Nutt	Taxaceae Taxaceae	Inhibition of tubulin stabilization	Kumar et al. (1997), Mans et al. (2000), Schwartzmann et al. (2001, 2000)
Etoposide, Teniposide	<i>Podophyllum peltatum</i> L. <i>Podophyllum emodi</i> Wall ex Hook. f. & Thomson	Berberidaceae Berberidaceae	Inhibition of topoisomerase II	Mans et al. (2000), Schwartzmann et al. (2001)
Irinotecan, Topotecan, 9-aminocamptothecin, 9-nitrocamptothecin Gemcitabine, Cytarabine	<i>Camptotheca acuminata</i> Decne. <i>Cryptotheca crypta</i>	Cornaceae Cornaceae	Inhibition of topoisomerase I	Mans et al. (2000) Schwartzmann et al. (2001)

mechanisms of action of luteolin have been proposed with respect to its anticancer properties; some of these include elevation levels of lipid peroxidation and activity of glutathione-S-transferase. Similarly, cannabinoids (isolated from *Cannabis sativa* L.) have been shown to inhibit the growth of tumour cells in culture and animal models by modulating key cell-signalling pathways (Guzman, 2003) and inducing direct growth arrest and death of tumour cells, as well as inhibiting tumour angiogenesis and metastasis; the receptors regulate cell-survival and cell death pathways differently in tumour and non-tumour cells.

Flavokawain A, B and C (naturally occurring chalcones isolated from several medicinal plants) are involved in the induction of cell cycle arrest in several cancer cell lines (Abu et al., 2013). Tang et al. (2010) showed that these compounds affected the cell cycle regulation of a p53-wild-type bladder cancer cell line and increased the amount of p21 and p27 cell cycle regulatory proteins and induced a G1 arrest. The authors further claimed that the molecular mechanism underlying this occurrence was the reduction of inhibitory kinases, Myt1, and Wee1.

The combinatorial effect of many compounds

isolated from plants has shown effective anticancer potentials; the most common being vinca alkaloids of *Cantharathus roseus* (L.) G. Don. Vinca leukoblastine and leurocristine (vincristine) are combined in cancer treatment (Dardi et al., 2012).

Antiproliferative activity, antioxidant capacity, and tannin content of plants from semi-arid North-Eastern Brazil were evaluated; 14 species were selected and methanol extracts assayed for antiproliferative activity against Hep-2 (laryngeal cancer) and NCI-H292 (lung cancer) cell lines using the (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazole) (MTT) method (de Melo et al., 2010); antioxidant activity was determined with 2,2-diphenyl-2-picrylhydrazyl (DPPH) assay, and the tannin content estimated by the radial diffusion method.

#### THE POTENTIALS OF NIGERIAN MEDICINAL PLANTS IN THE MANAGEMENT OF CANCER

Medicinal plants provide new and effective chemical molecules required to boost the immune system or to help fight foreign materials in the body. Secondary metabolites from plants are

good sources of new compounds of pharmaceutical importance. In many cultures, plants are used both as foods and medicines. The effectiveness of some of these food plants (many of which are used as dietary supplements) in the management of cancer has been evaluated by Cassidy (2003). Out of experimentation with local vegetation, indigenous cultures come up with varied use of vegetal species. However, various parts of plants have been reportedly used to manage many chronic and non-communicable diseases, such as cancer, cardiovascular and cerebrovascular diseases, stroke, age-related functional decline, Alzheimer's disease (Tan, 2010; Liu, 2003). Higher plants have provided pharmacologically active substances and these have been prescribed for many diseases over the centuries by traditional societies. Soladoye et al. (2010) reported ten recipes comprising 73 plants used in the management of cancer in Ogun State, Nigeria.

Complementary and alternative medicine (CAM) is now forming part of the medical and social circles. Patients are increasingly incorporating CAM (nutritional/dietary supplements, relaxation strategies, and various types of social support) into cancer prevention and treatment (DiGianni et

al., 2002). Several studies have reported the use of herbs or vitamins as part of their CAM regimen. Complementary and alternative cancer treatments are a diverse group of health care systems, practices, and products that are not part of conventional medicine. Most complementary and alternative medicines for cancer have now been rigorously studied or tested. The ethanol extract of *S. longepedunculata* from Osogbo, Nigeria induced DNA fragmentation in Ehrlich ascites carcinoma *in vitro* using Trypan blue assay and *in vivo* in tumour bearing mice (Lawal et al., 2012). Joloo (a traditional herbal formula used in the management of breast tumor in South Western Nigeria) was evaluated for its cytotoxic and antiproliferative activity by Oloyede et al. (2012). The authors used MTT assay to screen the cytotoxic and apoptotic activities of seven individual plants, as well as five fractionated portions of Joloo formulation. Baraya et al. (2014) reviewed five traditionally used medicinal plants for breast cancer treatment in Nigeria. The authors claimed that *Vernonia amygdalina* Delile was the most popularly used anticancer plant and the most studied. Ethnobotanical survey of folkloric plants used in the management of cancer (or breast cancer) has been conducted by previous authors in the field (Soladoye et al., 2010; Mohammed et al., 2014).

#### **A SURVEY OF TRADITIONAL RECIPES USED IN CANCER MANAGEMENT IN ABEOKUTA, OGUN STATE**

The study was conducted in Abeokuta, the capital city of Ogun State, Nigeria. Abeokuta lies on Longitude 3° 2' East and Latitude 7° 11' North. It is surrounded by large mass of rocks, and has a population of about one million people (Idu et al., 2010). The present day occupants are the Yorubas, but the original settlers were the Egbas, known for traditional arts, carving and sculpturing (Idu et al., 2010). The city is now densely populated as civil servants and traders now inhabit Abeokuta. The respondents were 10 female herb-sellers who claimed to have potent remedies for cancer management and were ready to divulge information on anti-cancer remedies. Informed consent was obtained from each respondent prior to interview. The interview was conducted in Yoruba. The local names of botanicals, plant parts, method of preparation of remedies and mode of administration of a remedy in treatment were documented (Sofowora, 1993). Twenty (20) botanicals from 16 families and 4 recipes with plausible anticancer action were recorded. The recipes used in the management of breast cancer in Abeokuta, Ogun State, Nigeria are presented in Table 3. Table 4 shows the profile of the 20 Nigerian plants used in the management of breast cancer. Four recipes consisting of twenty plants used in the management of breast cancer are reviewed in this study.

#### **A REVIEW OF 20 MEDICINAL PLANTS USED IN BREAST CANCER MANAGEMENT**

##### ***Alafia barteri* Oliv. – Apocynaceae**

*A. barteri* is a high climbing, scandent shrub with small white or pink flowers; it is reportedly used in the treatment of sickle cell anaemia, toothache, rheumatism, fever, and inflammation (Burkill, 1985). Leaf infusion and root decoctions are used in Nigeria and other African countries as a remedy for malaria (Olowokudejo et al., 2008). Phytochemical constituents of the ethanol extract of leaf and root showed the presence of total polyphenols, flavonoids, tannins, saponins, alkaloids and terpenoids (Lasisi et al., 2012). Hamid and Aiyelaagbe (2011) reported the presence of reducing sugars, glycosides, flavonoids and anthraquinones for all the extracts. Steroids from the ethylacetate and methanol extract. Only ethanol extract contained saponins. Adekunle and Okoli (2002) reported the antifungal properties of the ethanol and aqueous leaf extracts, while the antibacterial and antifungal properties of the hexane, ethylacetate and methanol extracts of the stem was investigated by Hamid and Aiyelaagbe (2011). Methanol extract showed inhibitory activity against *Escherichia coli* and *Pseudomonas aeruginosa* at 25 to 200 mg/ml, while the hexane and ethylacetate extracts showed inhibition against *E. coli* and *P. aeruginosa* at varied concentrations. The brine shrimp (*Artemia salina*) lethality assay for possible cytotoxicity was moderate. However, the leaf was higher in cytotoxicity as compared to the root fractions (Lasisi et al., 2012).

##### ***Allium ascalonicum* L. – Amaryllidaceae**

*A. ascalonicum* is an aromatic herb used for culinary purposes. It is an annual herb usually found in Nigeria and formed part of the dietary components of many African populations. It is also employed in many herbal remedies against pile, cancer, and in the treatment of central nervous disorders (Mohammadi-Motlagh et al., 2011; Akindele et al., 2012). Phytochemical analysis of hydro-ethanolic extract of the aerial part revealed the presence of alkaloids, tannins, glycosides, anthraquinones, phlobatannins, and flavonoids (Akindele et al., 2012). Based on the frequency of the plant in the result of ethnobotanical survey for the treatment of tuberculosis and non-tuberculosis mycobacteria diseases, Igbokwe et al. (2014) reported that the methanol extract of the plant showed significant inhibitory potential against 3 out of 4 mycobacteria species at 25 to 200 mg/ml with minimum inhibitory concentration (MIC) of 100 mg/ml. The organisms were *Mycobacterium fortuitum* ATCC 648, *Mycobacterium smegmatis* ATCC 19420, *Mycobacterium abscessus*, and *Mycobacterium phlei* ATCC 19240. Rattanachaiakunsopon and Phumkhachorn (2009) studied diallyl sulfide content and antimicrobial

**Table 3.** Herbal recipes used in the management of breast cancer in Abeokuta, Ogun State.

S/N	Prescription	Method of preparation	Use of remedy in regimen
1	<i>Kigelia Africana</i> fruit and <i>Capsicum frutescens</i> fruit	Decoction in water	The patient covers her body over the preparation exposing the breast to the steam from the preparation (fumigation); pus is seen to gush out from the breast.
2	<i>Triclisia subcordata</i> leaf; <i>Alafia barteri</i> leaf; <i>Olox subscorpioidea</i> root; <i>Clausena anisata</i> stem bark; <i>Tephrosia vogelii</i> stem bark; <i>Macaranga barteri</i> stem bark; <i>Calliandra portoricensis</i> root; <i>Anthocleista djalonensis</i> root; <i>Xylopia aethiopica</i> fruit and potash.	Decoction in water	A cup (50 cl) of the preparation is taken two times daily after food.
3	<i>Olox subscorpioidea</i> root; <i>Plumbago zeylanica</i> root; <i>Tetrapleura tetraptera</i> fruit; <i>Allium ascalonicum</i> leaf; <i>Khaya ivorensis</i> stem bark; <i>Lophira alata</i> root; <i>Alstonia congensis</i> stem bark; <i>Grewia flavescens</i> root; and <i>Xylopia aethiopica</i> fruit.	Infusion in cold water	The extract (25 cl) is taken orally three times daily. Also the extract is used for bathing the breast daily.
4	<i>Erythrophleum suaveolens</i> stem bark; <i>Allium ascalonicum</i> ; and <i>Tetracera alnifolia</i> root.	Soap and cream	The ingredients are ground; half of the preparation is added to palm kernel oil "adi eyan". The remaining half is added to traditional black soap. The soap is used for bathing the breast and the oil as cream after bath.

activity of shallot oil against food-borne pathogenic bacteria. The authors reported that the oil and all the four major diallyl sulphides inhibited all of the test bacteria, namely, *E. coli* 0157:H7, *Listeria monocytogenes*, *Salmonella enterica*, *S. aureus* and *Vibrio cholerae*. The antioxidant and antibacterial activity of the plant has been reported by Mnayer et al. (2014). The aqueous extracts of *A. ascalonicum* induced suppression of cancer cell lines' proliferation. Furthermore, Shallot could be a candidate for the prevention and treatment of many diseases related to inflammation and malignancy (cancer) (Mohammadi-Motlagh et al., 2011).

#### ***Alstonia congensis* Engl. – Apocynaceae**

*A. congensis* is a tree to over 30 m high of the evergreen forest in damp situations. It is found in

Southern Nigeria, and extending to Zaire and Cabinda. It occurs from South Western Nigeria to the Central African Republic, Eastern and Southern DR Congo, and Northern Angola. The tree is very similar in general appearance to *A. boonei* and it is probable that it has the same folk medicinal applications. Different parts of the plant have been used for therapeutic purposes in some countries in Africa. A stem bark decoction is used for the treatment of malaria, gonorrhoea, diarrhoea, and other gastro-intestinal problems. The bark is used as anti-poison and anthelmintic. The latex is valuable in the treatment of headache and skin infections, such as ulcers, scabies and yaws.

The leaves are lightly roasted and smoked as remedy for cough (Burkill, 1985). Traditionally, the plant is used to treat headache, intestinal problems, rheumatic pain, ulcer and diarrhoea (Kayode et al., 2009). In the treatment of diabetes,

equal proportion of *A. congensis* bark and *X. aethiopica* fruit is consumed. Phytochemical screening indicated the presence of alkaloids and polyphenols (Ogbonnia et al., 2008). *A. congensis* contains various alkaloids (Evans, 2002). About fifteen (15) alkaloids have been isolated from the ethanolic stem bark extract (Majekodunmi et al., 2008).

Indole alkaloid echitamine is one of the several alkaloids isolated from the bark and leaves of the plant and it has several pharmacological activities (hypotensive activity and relaxing activity of smooth muscles), but the compound displayed limited antiplasmodic effect. The leaves and bark showed cardio-activity in animal tests (Ilesanmi et al., 1988). The methanolic leaf extract displayed some antimalaria activity against *Plasmodium berghei* in mice (Awe and Poeke, 1990). Acute and sub-acute toxicity of *A. congensis* bark and *X. aethiopica* fruit mixtures in Swiss albino rats

**Table 4.** Profile of botanicals used in the regimen of breast cancer in Abeokuta, Ogun State.

S/N	Botanical	Family	Common name	Local name			Part used	Habit
				Yoruba	Igbo	Hausa		
1	<i>Alafia barteri</i> Oliv.	Apocynaceae	Guinea-fowl's crest	Agbari etu	Obomba	-	Leaf	Shrub
2	<i>Allium ascalonicum</i> L.	Amaryllidaceae	Shallot	Alubosa elewe	-	Albara mai wuyaa	Leaf	Herb
3	<i>Alstonia congensis</i> Engl.	Apocynaceae	Stoolwood	Ahun	-	-	Stem bark	Tree
4	<i>Anthocleista djalensis</i> A. Chev	Gentianaceae	Cabbage tree	Sapo	Akpakoro	Putaa	Root	Tree
5	<i>Calliandra portoricensis</i> (Jacq.) Benth.	Fabaceae	Calliandra	Tude	-	-	Root	Shrub
6	<i>Capsicum frutescens</i> L.	Solanaceae	Chilli pepper	Ata were	Ose mkpele	Barkoono	Fruit	Herb
7	<i>Clausena anisata</i> (Willd) Hook f. ex Benth	Rutaceae	Clausena	Atapari obuko	-	-	Stem bark	Shrub or small tree
8	<i>Erythrophleum suaveolens</i> (Guill & Perr)Br	Fabaceae	Sasswood	Obo	Nyi/Ihi	Gwaska	Stem bark	Tree
9	<i>Grewia flavescens</i> Juss.	Malvaceae	Sandpaper	Okere	-	-	Root	Shrub
10	<i>Khaya ivorensis</i> A. Chev.	Meliaceae	African Mahogany	Oganwo	Ono	Male	Stem bark	Tree
11	<i>Kigelia africana</i> (Lam.) Benth	Bignoniaceae	Sausage tree	Pandoro	Uturubein	Rawuya	Leaf and Fruit	Tree
12	<i>Lophira alata</i> Banks ex C.F. Gaertn.	Ochnaceae	Red iron wood	Owo	Aba	Kujeme	Root	Tree
13	<i>Macaranga barteri</i> Mull. Arg.	Euphorbiaceae	Macaranga	Asasa	Owariwa	-	Stem bark	Shrub
14	<i>Olax subscorpioidea</i> Oliv.	Olacaceae	Olax/Stink ant	Ifon	Atu-ogili	Gwaanon kurmii	Root	Shrub or tree
15	<i>Plumbago zeylanica</i> L.	Plumbaginaceae	Ceylon leadwort	Inabiri	Anaya-aku	-	Root	Shrub
16	<i>Tephrosia vogelli</i> L.	Fabaceae	Fish bean	Oronbeje	-	Shibi	Stem bark	Shrub
17	<i>Tetracera alnifolia</i> Willd.	Dilleniaceae	Tetracera	Opon	-	-	Root	Climber
18	<i>Tetrapleura tetraptera</i> (Schum&Thonn)Tau	Fabaceae	Tetrapleura	Aidan	Okpokrikpo	-	Fruit	Tree
19	<i>Triclisia subcordata</i> Oliv.	Menispermaceae	Triclisia	Alugbonran	-	-	Leaf	Climber
20	<i>Xylopia aethiopica</i> (Dunal.) A. Rich	Annonaceae		Eeru alamo	Uda	Kimbaa	Fruit	Trees

based on the claimed use in the treatment of diabetes, revealed the tendency of kidney problems on a long term use (Ogbonnia et al., 2008).

#### ***Anthocleista djalensis* A. Chevy – Gentianaceae**

*A. djalensis* is a tree which grows up to 15 m high; bole up to 4 cm in diameter, twig sometimes erect with spines above the leaf axils (Jensen and Schripsema, 2002). The cabbage tree has opposite obovate leaves, spiny branches and

white flowers. It occurs from Guinea Bissau east to Cameroun. The seeds and bark are used for their antipyretic, stomachic and purgative action. The bark is a tonic and it contains alkaloids (brucine) and glycosides (loganin) (Oliver, 1960). The root bark contains alkaloids, inulins, saponins, and dlycoside-loganin. The decoction of the bark is used to cure skin diseases, such as eczema and rashes (Gill, 1992). A decoction of the leaves with lemon is used as a remedy for epilepsy and diuretic (Oliver-Bever, 1986). The extracts from the leaves, roots and stem have been used traditionally to treat wound, constipation, dysentery, diarrhoea, hepatitis, skin

infection, inflammation, etc. (Okoli and Iroegba, 2004; Aiyeloja and Bello, 2006). Phytochemical screening of the methanol, petroleum ether and hot-water leaf extracts showed the presence of tannins, saponins, flavonoids, steroids, terpenoids, and cardiac glycosides (Akinyemi and Ogundare, 2014). Phtalide, xanthones, monoterpene-diol, djalonenol as well as iridoid glucoside, djalonenoside have been isolated from the plant (Onocha et al., 2003). *A. djalensis* root extract and fractions (37 to 111 mg/kg) caused reduction in fasting blood glucose levels in alloxan-induced diabetic rats both in acute and prolonged treatment (2 weeks). The extract and

fractions were more active than the reference drug (glibenclamide). The results suggest that the plant could be a good candidate in the management of diabetes (Okokon et al., 2012). Bassey et al. (2009) reported that the leaf extract of the plant exhibited a significant antiplasmodial activity against *Plasmodium beighei* both in the 4-day early infection test and in established infection. Also, the authors reported that the stem bark extract also demonstrated a promising blood schizontocidal activity in early and established infections. *A. djalensis* root extract contained saponins, flavonoids, tannins, reducing sugar, steroids, phlobatannins, volatile oils, and alkaloids. The extract was active against *E. coli*, *S. typhi* and *Staphylococci* (Leke et al., 2012). Akinyemi and Ogundare (2014) also validated the antibacterial of the plant. The antimycobacterial activity of the root and leaf extracts against *Mycobacterium smegmatis* was reported by Esimone et al. (2009). The methanol extract and aqueous fraction of the plant had acute anti-inflammatory activity (Okunrobo et al., 2008). The aqueous extract of *A. djalensis* has been reported to have hypertensive effect in rats as well as increase the time and amplitude of rabbit duodenal movement (Okoli and Iroegba, 2004).

#### ***Calliandra portoricensis* (Jacq.) Benth. – Fabaceae**

*C. portoricensis* is large, multiple-trunked, low-branching, evergreen shrub with silky leaflets that are glossy copper when new, turning to a dark metallic green. The profuse, fragrant bloom is the main reason for its popularity, with big puffs, two to three inches across, of watermelon pink, deep red, or white silky stamens, produced during warm months (Burkill, 1985). It is a native from tropical America usually cultivated in gardens for ornamental purposes. The dried leaves are sniffed to induce sneezing to relieve headache. The decoction of *C. portoricensis* roots and ginger are used for constipation, enema, lumbago pain, and as purgative (Gill, 1992). The sap of the plant is irritant and is applied to the eyes of a moribund person to test for prospect of recovery; hence, the Twi name of the plant as “nyamafunu” meaning to wake a corpse. The root is pungent and probably strongly purgative. The powdered root is mixed with pepper for the treatment of gonorrhoea (Burkill, 1985).

Phytochemical analysis of plants in the genus revealed the presence of tannins, flavonoids and saponins (Zeid et al., 2007). The chemical constituents of *C. portoricensis* include betulinic acid, lupeocaffic acid, astilbin, catechin-3-O-rhamnoside, and p-hydroxybenzoic acid (Nia et al., 1999). The leaves of *C. portoricensis* are used as antimicrobials in the treatment of skin infections. The anti-inflammatory, anticonvulsant, immunomodulatory and ulcerogenic activity have been investigated in the genus *Calliandra*. The immunoadjuvant activity of the butanolic extract from the aerial parts of *C. portoricensis* was

reported by Barbosa (2014). Ethanolic root extracts of *C. portoricensis* reversed sickled blood at varying concentrations (Barbosa, 2014). Yoshiki et al. (1996) reported the antitumoral and anti-HIV activity of betulinic acid isolated from the plant. The antioxidant activity of galloylated flavanol glycosides has been confirmed by Moharram et al. (2006). The ethanol extract of *C. portoricensis* root showed moderate inhibitory activity against *Salmonella typhi* and high activity against *Pseudomonas aeruginosa* (Gbadamosi, 2012). Chronic administration (28 days) of *C. portoricensis* leaf extract may inhibit the proper function of the stomach and pancreas in mice (Ofusori et al., 2011).

#### ***Capsicum frutescens* L. – Solanaceae**

*C. frutescens* is a well used tropical and subtropical medicinal plants. It can be annual or short-lived perennial plants. Flowers are white with a greenish white or greenish yellow corolla, and are either insect- or self-pollinated. The plants' berries typically grow erect; ellipsoid-conical to lanceoloid shaped. It is usually very small and pungent, growing 10 to 20 mm long and 3 to 7 mm in diameter. Fruit typically grows a pale yellow and matures to a bright red, but can also be other colours. It has a pungent principle in the fruit and seed, and hence used as a spice. It is now dispersed world-wide under cultivation in many varieties and cultivars, and present in West Africa mainly north of the forest zone. The leaf sap is squeezed into the eyes as headache cure and for conjunctivitis. The leaf-macerate with citron juice is instilled to weeping ears and as a dressing for wound, sores as well as poultice for boils (Burkill, 1985). The fruit is eaten to relieve muscle, joint, and toothache pain; to treat cough, asthma, and sore throat. Also used as stimulant, and to treat stomach ache, sea-sickness, and flatulence (Francis, 2005).

The plant improves natural warmth and blood circulation; it is taken in ordinary cold, fever and dysentery. It forms part of remedies for the treatment of malaria and gonorrhoea (Gill, 1992). *C. frutescens* contains octopamine, a phenolic amine related to tyramine (Burkill, 1985). The plant has been evaluated and found to contain hydrobenzoic acid, hydroxycinnamic acid and ascorbic acid. It acts as stimulant; accelerates oxygenation of cells; encourages the production of corticosteroids (Vinayaka et al., 2010). The fruit contains 1% of capsaicin (Hill and Sharma, 1996). The carminative, antispasmodic and antiseptic properties have been evaluated. The ripe fruits of the plant contained essential oil, alkaloids, glycosides, phenolic compounds, terpenoids, and flavonoids. It had antimicrobial and antioxidant activities due to the chemical contents (Nascimento et al., 2013). Sambo et al. (2007) reported the mechanism of action of extracts of *C. annum* and *C. frutescens* on gastric acid secretion in



rats. *C. frutescens* may serve as source of natural bactericidal agent to be used in food and medicinal system due to the observed antibacterial effects (Koffi-Nevry et al., 2012).

#### ***Clausena anisata* (Willd.) Hook f. ex Benth – Rutaceae**

*C. anisata* is a tropical shrub or small tree up to 6 m high with strongly scented leaves. It is commonly found in coaster thickets, forest undergrowth and in savannah. The plant is native to tropical Africa. The decoction of *C. anisata* leaves is traditionally used in the treatment of malaria, rheumatism, constipation, dysentery, asthma, oral infections, and skin infections. It also finds application in the management of epilepsy and as an anticonvulsant. Fresh leaves burnt are used as mosquito repellent. Also, the leaves are used as antiseptic and antimicrobial in skin diseases such as measles, chicken pox, wound and sores. The bark of the plant appears to have no medicinal usage (Burkill, 1985). The alkaloids clausenol and clausenine have been isolated (Arbab et al., 2012). The chemical constituents of the stem led to the isolation of two new carbazole alkaloids (Ito et al., 2009). Other phytochemicals present in *C. anisata* are coumarins and other derivatives. The young leaves contain 1.2-7.1% volatile oil and are readily inflammable (Burkill, 1985). Hydrodistilled leaves yielded 0.55% of oil with phenylpropanoids and anethone as the most abundant compound. Other components of the oil are sabinene, germacrene-D, germacrene-B, ocimene etc. Antimicrobial activity of the essential oil was studied against clinically isolated strains of both Gram positive and Gram negative bacteria. The oil was more active against *Pseudomonas aeruginosa* and *Salmonella typhimurium* with MIC values 125 and 250 µg/ml, respectively (Senthilkumar and Venkatesalu, 2009). The essential oil of *C. anisata* contains five major compounds and has remarkable larvicidal properties (Govindarajan, 2010). Mogale et al. (2012) reported the effects of leaf extracts of the plant on selected diabetic related metabolizing enzymes.

#### ***Erythrophleum suaveolens* (Guill. & Perr.) Brenan – Fabaceae**

*E. suaveolens* is a perennial tree of about 30 m in height, slightly buttressed often low-branching and producing a dense spreading crown. It is a native to Africa and introduced as an ornamental to tropical Asia. The bark contains alkaloids (0.3 to 1.5%), namely, cassamidine, erythrophlamide and erythrophleine and procyanidins (polyphenols). The bark has antioxidant effect due to procyanidins content and its extract has excellent local anaesthetic activity on skin. The alkaloids have stimulant effect on the heart (short-lasting), strong diuretic effect and increase contractions of the intestine and uterus

(Burkill, 1985). The stem bark decoction is used as emetic and purgative, as an anaesthetic, antimalarial and as anthelmintic; for skin infections, rheumatism and wound (Akinpelu et al., 2012). The plant does well as rodenticide, insecticide and in tanning of hides and as dye (Aiyegoro et al., 2007). The bark decoction is also used for dressing wounds, chicken pox, gangrenous sores and swellings (Gill, 1992). Saponin from the ethanolic extract of *E. suaveolens* stem bark was found to be toxic to fresh water snails (*Lanites lybicus*). The treatment caused inhibition of acetylcholinesterase activity in the haemolymph, muscle, hepatopancreas, and intestine of the snails in a dose-dependent manner (Akinpelu et al., 2012). Akanji and Sonibare (2015) confirmed the wound healing activity of ethanol extract of the stem bark on infected albino rats. The cold water crude extract of the stem bark has the potential of been developed as an antimotility agent as a remedy for gastrointestinal problems (Ogundeko et al., 2014). Ngoupayo et al. (2015) reported the antioxidant activity of stibenoid and flavononol isolated from the stem of *E. suaveolens*.

#### ***Grewia flavescens* Juss. – Malvaceae**

*G. flavescens* is a multi-stemmed herbaceous sub-shrub, dwarf of 1.5 m high; its bark is dark grey-brown. The main stem is 4-angled and deeply grooved. The light green *G. flavescens* has beautiful, bright yellow and sometimes fragrant flowers. It is a frost-resistant, hardy shrub or small tree that is adaptable to all soils, from clay to sand, and does not require much water. It is native of Central America, now dispersed to West Africa (Burkill, 1985). The fruit has irritant, vesicant and rubefacient properties. *G. flavescens* is reported to be useful as medicinal agent to treat several diseases such as hypertension, rheumatism, and swollen feet, dermatitis, diarrhoea, gonorrhoea and urinary complaints. The fruits can be eaten when ripe and still fresh, and can also be made into fermented drinks. Lactating mothers are fed with the sweetened fruit extracts to improve their health conditions and lactating ability (Goyal, 2012). The plant is grown for its fruits as condiment to food and it contains alkaloids (solanidine and solasodine). It is also rich in vitamins A, C, and E (Burkill, 1985). Triterpenoids, triacontanol, and  $\beta$ -sitosterol have been isolated from the roots (Prakash and Singh, 1981). There is dearth of information on the pharmacological effect of the plant.

#### ***Khaya ivorensis* A. Chev. – Meliaceae**

*K. ivorensis* is an evergreen or deciduous, monoecious, large to very large tree up to 60 m tall; bole branchless for up to 30 m, usually straight and cylindrical, up to 160 (-210) cm in diameter, with large buttresses up to 2 (-4 m) high, sometimes extending into prominent surface roots. It is found in Angola, Cameroon, Côte d'Ivoire, Gabon,

Ghana, Liberia, and Nigeria where it grows primarily in lowland tropical rainforests. It is a popular traditional African medicinal plant. The bark, roots and leaves are traditionally used for the treatment of various ailments including several infectious diseases. A decoction of the bitter bark is used for the treatment of fever, tumours, dysentery, rheumatism, cough, and anaemia. It is also used as an enema for dysentery (Burkill, 1985). It has antimalarial and anti-inflammatory properties; in Cameroun, the stem bark decoctions of *K. ivorensis* and *Erythrina senegalensis* are used in the treatment of malaria (Sofowora, 2008). In central Cameroun, however, the combined decoction of *K. ivorensis* and *Alstonia boonei* is used as a prophylactic antimalarial (Tepongning et al., 2013). Chemical analysis of *K. ivorensis* revealed the presence of limonoids (Zhang et al., 2009). Two new limonoids were isolated from the fruits by Kai-Long et al. (2014). Abdelgaleil et al. (2005) isolated ten limonoids from the stem bark of the plant and validated the antifungal activities of the compounds against *Botrytis cinerea*, *Aspergillus niger*, *Monilinia fruticola*, *Rhizopus stolonifer*, *Geotrichum candidum* and others. Limonoids from fruits of *K. ivorensis*, namely, 3-O-methylbutyryl seneganolide A, Seneganolide and 1, 3-dideacetylkhivorin exhibited cytotoxicity against certain tumor cell lines (Ji et al., 2014). In a study of the quantitative effect of *Piliostigma thionnigii* and *K. ivorensis* (singly or combined) against dry yam, Babajide et al. (2008) validated the antimicrobial activities of leaves of the two plants against organisms isolated from the dry yam. Zhang et al. (2012) reported the immunosuppressive effect of macrolide from the plant. The antiplasmodial activity of the aqueous extracts of the stem bark has been assessed in mouse model (Tepongning et al., 2013). Other reported pharmacological activities of the plant are as follows: anti-inflammatory and toxic effect of its stem bark on rats (Agbedahunsi et al., 2004); antimalarial activity (Bickii et al., 2000).

#### ***Kigelia africana* (Lam.) Benth – Bignoniaceae**

*K. africana* has a short, squat trunk with light brown, sometimes flaky bark and supports a dense rounded to spreading crown (18 m high and 20 m wide) of leathery, slightly glossy foliage (deciduous). The huge, grey-brown fruits, 800 × 120 mm hang from long stalks, from December (summer) to June (winter) (Burkill, 1985). The tree is widely grown as an ornamental tree in tropical regions for its decorative flowers and unusual fruit. It is widely distributed in the South, Central and West Africa, and other parts of the world. It is found mostly in wetter areas and spread abundantly across wet savannah and riverine areas (Sofowora, 1982). The plant is used in the treatment of gonorrhoea (root bark), post partum haemorrhage (fruits and roots), and the leaves and stem bark are used for malaria, kidney disorder, stomach

trouble, dysentery and infectious diseases (Gill, 1992). The fruits used as a dressing for ulcers, as purgative and aphrodisiac. The doctrine of signature has been applied to the shape of the fruit, and as such, the fruits and barks are used to grow breast and as botanical galactogogues (Oliver-Bever, 1986; Grace et al., 2003). As botanical galactogogues, the ripe fruit of *Kigelia africana* is made into a paste and massaged on the breast; furthermore, the authors reported that a decoction (200 ml) of the fruit is taken twice daily to induce secretion of breast milk (Gbadamosi and Okolosi, 2013). The infusion of the stem bark or root powder is used in the management of ulcer and pneumonia (Irvine, 1961). The unripe fruit is confirmed to be useful as a remedy for rheumatism and haemorrhoids. Other traditional uses include the use of the bark to remedy sexually transmitted diseases, and in the dressing of wounds. Secondary metabolites, such as iridoids, flavonoids, coumarin derivatives, lignans, sterols, naphthaquinones, etc., have been reported in *K. africana* (Asekun, 2006; Gormann et al., 2004). Pharmacological activities of the plant reported are antifungal, antibacterial, antineoplastic, analgesic, anti-inflammatory, antimalarial, CNS stimulant, antiprotozoal, and antidiarrheal activities (Saini et al., 2009); anti-aging, anticancer and antioxidant potentials (Gabriel and Olubunmi, 2009) and anti-leprosy activity (Lal, 1983). The wood extract has been evaluated against drug-resistant strains of *Plasmodium falciparum* for antimalarial activity (Carvalho et al., 1988). Olaleye and Rocha (2008) reported the *in vitro* and *in vivo* antioxidant activity of *K. africana*. Santos et al. (2013) confirmed the anti-ulcer potential of aqueous extraction of the plant against ethanol-induced ulcer in rats. *K. africana* leaf ethanol extract (450 mg/kg body weight) gave the best results in ulcer index evaluation on aspirin-induced ulcerogenic animals (Orole et al., 2013).

#### ***Lophira alata* Banks ex C.F. Gaertn. – Ochnaceae**

The trunk of *L. alata* is usually straight, without buttress roots, but sometimes with a swollen base, and is usually clear of branches up to about 30 m (98 ft). It is a deciduous tree of up to 60 m tall (Burkill, 1985). *L. alata* is found in the subtropical and tropical moist lowland forests of Cameroun, the republic of Congo, Ivory Coast, Equatorial Guinea, Gabon, Ghana and Nigeria; it has a single trunk and no branching near the ground (Hairu et al., 2013). The bark is used to treat convulsions, epilepsy, eye problems, and yaws. The leaves are used to treat respiratory diseases, gastrointestinal disorders, fever, cough, and jaundice. Ten plants (including *L. alata*) used in Yaoundé in Cameroun were tested for biological activity (Pierne et al., 2008) against Gram positive and negative bacteria and two groups of fungi. Traditionally, the bark is used in treatment of inflammation, toothache and as analgesic. In South Western Nigeria, Kayode (2006) reported the use of the leaves, stem bark, root

and seed in the treatment of malaria. Twigs are used as toothbrush. The seed contains fixed oil (mene oil). Tih et al. (1994) reported the isolation of lophirosides and related groups from the stem bark of *L. alata*. Phytochemical analysis of *L. alata* indicated the presence of alkaloids, tannins, saponins, anthocyanosides and reducing compounds; cardiac glycosides and anthraquinones were absent. Gas Chromatography-Mass Spectrometry (GC-MS) analysis of stem bark extract revealed the presence of 12 volatile organic compounds with varying percentage peak area (Haliru et al., 2013). A list of potential antimalarial plants including *L. alata* from Nigeria has been provided by Adebayo and Krettli (2011). Tetraflavonoid isolated from methanol extract of the stem bark inhibited tumour promotion in mouse (Murakami et al., 1992). Iniagbe et al. (2014) validated the neuropharmacological properties of the aqueous extract of stem bark of the plant in animal models. The acclaimed anticancer activity of the plant may be attributed to lophirones B and C in the stem bark (Ajiboye et al., 2014).

#### ***Macaranga barteri* Mull. Arg. – Euphorbiaceae**

*M. barteri* is a shrub or tree of 20 m high by 1.30 m girth. It is common in Guinea, Southern Nigeria and Equatorial Guinea (Burkill, 1985). In Nigeria, the plant is used as a vermifuge and febrifuge; to relieve cough and bronchitis (Adesegun et al., 2007). In Sierra Leone and Ivory Coast, the leaves are used for the treatment of gonorrhoea and as anti-anaemic tonic, respectively. The leaf is also used in the treatment of ulcer, stomatitis and against amnesia (Oliver-Bever, 1986). The decoction of the bark is used for dysentery and black tongue. It is chewed for bad breath and as an appetizer. It is also valuable for the treatment of cough, swellings, bruises, boils, and headache. The plant contains inulins saponins and tannins (Gill, 1992). Phytochemical investigations of the leaves by Adesegun et al. (2007) revealed the presence of saponins and phenolic compounds; alkaloids, anthraquinones, cardiac, and cyanogenic glycosides were not detected. Steroids, tannins, coumarins, and methyl gallate (all of different classes) have been isolated from the stem bark (Ngoumfo et al., 2008). *M. barteri* is a potential source of antioxidants. It showed strong inhibition of lipid peroxidation in linoleic acid system and moderate reducing properties (Adesegun et al., 2007). The anti-inflammatory activity of the methanol extract of the stem bark was also evaluated in a cell-based respiratory burst assay (Ngoumfo et al., 2008).

#### ***Olax subscorpioidea* Oliv. – Olacaceae**

*O. subscorpioidea* is a tree or sometimes a many-stemmed shrub up to 10 m high of deciduous forest; as

undergrowth in jungles or as thickets in savanna, and widely found across the region of Senegal to West Cameroun. Traditionally, the plant serves social as well as religious purposes. The leaf extract is used as anti-venom against snake bites and scorpion stings. The leaf, bark, and root are used in the treatment of venereal diseases, arthritis, rheumatism, and as febrifuge (Oni, 2010). Twigs used as chew-sticks. The berries are generally used as food. Alkaloids, glycosides, saponins, and steroids have been confirmed to be present in the root. The chemical composition, mineral constituents, and anti-nutritional factors of seeds have been evaluated (Otori and Mann, 2014). The non-nutrient composition (anti-nutrient factors) include phytate (24.2 mg/100 g), oxalate (21.3 mg/100 g), tannin (22.2 mg/100 g), cyanide (20.5 mg/100 g), flavonoids (19.6 mg/100 g), alkaloid (20.7 mg/100 g), and saponin (23.2 mg/100 g). The fatty acid profile of the seed oil revealed 100% saturation; significant amount of essential mineral was discovered in powdered seed samples. The amino acid content compared well with WHO standards (Otori and Mann, 2014). In a study on the *in-vitro* effect of the plant on monoamine oxidase activity from rat brain, Oni (2010) reported that the aqueous extract of *O. subscorpioidea* leaves significantly inhibited (53.2%) monoamine oxidase. The antimicrobial activity of the stem of the plant (Ayandele and Adebisi, 2007); anti-depressant effect of the leaves (Adeoluwa et al., 2014); and toxicological effects of the leaves (Adebayo et al., 2014) have been reported.

#### ***Plumbago zeylanica* L. – Plumbaginaceae**

*P. zeylanica* is a perennial shrub with glabrous, striate, and woody stems. It is spreading, herbaceous, suffrutescent plant, 1 to 2 m in length. The plant is found in the thickets, village environs and roadsides. It is widely distributed in Africa, Asia, and the Pacific. Traditionally, the root paste has been used to get relief from headache when applied to the forehead. It is also used in the treatment of skin diseases, muscular pain, and influenza. Leaves are used to treat leprosy and are also reported to have anti-rheumatic properties. The roots are used as expectorant and in the treatment of gastrointestinal diseases. The root is also used as an abortifacient and in treatment of dysentery; as aphrodisiac and in the management of scabies. The root is also good as an anti-atherosclerotic and for anti-fertility (anti-ovulation) (Burkill, 1985; Wabale, 2007). The chemical constituents reported include plumbagin, droserone, zeglamine, and other derivatives (Akhtar et al., 1992). Phytochemical screening of the root extracts prepared in different solvent (amyl alcohol, ethanol, methanol, ether, chloroform and distilled water) confirmed the presence of alkaloids, carbohydrates, flavonoids, tannins, steroids, and saponins (Subhash et al., 2013) with varying qualitative

characters. Antibacterial activity showed maximum inhibition against *Staphylococcus aureus* and *Bacillus subtilis* with methanol extract and minimum activity with ethanol extract. A comprehensive review of the pharmacological activities of the plant reported its antimicrobial, antiplasmodial, anticonvulsant, antioxidant, anti-fertility, anti-inflammatory, anti-arthritic, and wound healing activities. Furthermore, the cytotoxic and genotoxic effects were documented (Singh et al., 2011; Mandaokar and Jalalpure, 2011). Also, Aziz et al. (2008) reported the cytotoxic activity of the bioactive marker (plumbagin) on the growth and invasion of prostate cancer.

### ***Tephrosia vogelii* L. – Fabaceae**

*T. vogelii* is a soft woody-branching shrub with dense foliage reaching up to 0.5 to 4 m high. It has pinnate leaves and conspicuous red-or violet-purple flowers in terminal racemes. The plant is often cultivated (Oliver, 1960). The seed and leaves are used to improve soil fertility; and also as firewood (Kabera et al., 2014). Traditionally, the plant is used to treat ecto- and endoparasites in cattle (Hoffman, 2003). Other ethnoveterinary uses include the use of the plant in the treatment of skin infections and intestinal worms. It is used as an insecticide as well as poison to harvest fish (Farida and Vander, 1997). The plant might be used in combating schistosomiasis (bilharziasis) due to its activity against the hosts (snails) of the parasite. Leaves are used as molluscicides to kill intermediate host of bilharzias. The decoction of the leaves is also used as vermifuge, diuretic, and as cough remedy (Oliver, 1960; Gill, 1992). Rotenone isolated from the leaves has been found to be toxic to aquatic organisms (Agbon et al., 2004). Sesquiterpene, lignin, and rotenoid are classes of chemical compounds isolated from the plant (Wei et al., 2009). Phytochemical analysis of leaf extract indicated the presence of alkaloid, tannin, saponin, cardiac glycoside, rotenone, steroids, balsam, phenol and volatile oil (Akpa et al., 2010), quinines, leucoanthocians, anthocians, and anthraquinones (Kabera et al., 2014). Antibacterial activity of the leaf extract has been evaluated against *Bacillus subtilis* and *S. aureus*. The anthelmintic properties of the leaf crude extracts of the plant against gastrointestinal nematodes in goats have been evaluated by Kabera et al. (2014), and against *Ascaridia galii*, a chicken parasite (Siamba et al., 2007). Li et al. (2010) reported the free radical scavenging potential of the ether extract of the seeds, whereas the seeds possess antimicrobial and bacteriostatic activities. In cats, the antihypertensive property has been evaluated (Auda et al., 2009). The acute toxicity of leaf extract on *Tilapia zilli* has been evaluated by Akpa et al. (2010). Larvicidal activity of deguelin (a chemical compound from the leaf) has been reported and the abnormal behaviour

displayed by exposed fish increased with increasing concentrations of leaf extract of *T. vogelii* (Muiva, 2012).

### ***Tetracera alnifolia* Willd. - Dilleniaceae**

*T. alnifolia* is a liane or multi-stemmed climber up to 20 m high or shrubby tree to about 8 m, or trailing in grassland; of savanna, thickets, forest margins, and mangrove communities by coastal swamps, recorded from Senegal to West Cameroon, and also extending to Angola. The stem sap is used for the treatment of cataract, conjunctivitis, and other eye troubles. The sap is also used as a galactogogue. The leaf and stem are valuable in the treatment of dysentery, abdominal pain, rheumatism, hernia and haematuria. It is also used as vermifuge and purgative (Burkill, 1985). The decoction of the root is given for gonorrhoea, rickets, and as enema (Gill, 1992). The bark together with *Xylopia aethiopica* fruits, *Trema occidentalis* bark, and *Harungana madagascariensis* bark boiled in water is commonly used in the treatment of anaemia in South Western Nigeria (Gbadamosi et al., 2012). The leaf is used in the treatment of various diseases and infections. The sap resulting from the maceration of the lianous stem is anti-leprosy; leaf decoction is taken to treat dysentery (Oliver-Bever, 1986). Phytochemical screening revealed the presence of saponin and cardiac glycosides. Alkaloids and tannins tested negative. Flavonoids and coumarin derivatives have been isolated from *T. alnifolia* (Akendengwe et al., 2003). *In vitro* antibacterial activity was evaluated against *Mycobacterium tuberculosis* (Lawal et al., 2011) using WABA assay method. The hexane and chloroform extracts of root bark of *T. alnifolia* had anti-Mtb activity with MIC <100 µg/ml. Lawal et al. (2014) also reported the antimicrobial activity of crude extracts of leaf and root of the plant.

### ***Tetrapleura tetraptera* (Schum & Thonn.) Taub. – Fabaceae**

*T. tetraptera* is a robust perennial and deciduous tree of 20 to 25 m in height, with grey-brown and smooth-rough bark, with four longitudinal wing-like pods nearly 3 cm broad. The fruit possesses a characteristic pungent aromatic odour. The fruit is rich in sugar and may be used in flavouring food. The plant is native to Africa (Burkill, 1995). An infusion of the fruit is used as tonic, stimulant, anti-rheumatic, anticonvulsant and to treat gonorrhoea. The bark is used as purgative and emetic (Oliver-Bever, 1986). The fruit contains sugars, tannin and saponin. The bark contains aminopropionic acid derivative and the alkaloid mimosine (an irritant substance) (Oliver, 1960). *T. tetraptera* fruit together with *Senna alata* leaves and *Xylopia aethiopica* fruits is used in form of soap in the treatment of skin infections (Gbadamosi

and Oyedele, 2012). In the treatment of neonatal jaundice, the pod of *T. tetraptera* is mixed with traditional black soap and used for bathing; a decoction of pod is also used for bathing (Gbadamosi and Obogo, 2013). The plant is used in the treatment of epilepsy (Kadiri et al., 2013). Dichloromethane extract of the root bark had significant antiplasmodial activity *in vitro* (Lekana-Douki et al., 2011). In Nigeria, the fruits have been reported to have nutritional and anti-inflammatory, analgesic and antimicrobial properties. The fruits contain triterpenoids and flavonoids. The fruits are also used to protect food crops against pests. The decoction of the bark is used to treat stomach-ache, fever, headache, and to stop vomiting (Ojewole, 2005). The plant has many pharmacological values: its cardiovascular, neurovascular, hypotensive, anti-convulsant, anti-inflammatory, hypoglycaemic, and antimicrobial activities have been reported (Aladesanmi, 2007). The antiplasmodial activity of dichloromethane and methanolic extracts tested on *Plasmodium falciparum* strains: FCB (chloroquine-resistant) and 3D7 (chloroquine-sensitive) and on fresh clinical isolates using double-site enzyme-linked lactate-dehydrogenase immuno-detection (DELI) assay revealed interesting bioactivity (Lekana-Douki et al., 2011). The fruit exhibited wound-healing effect (Effiong et al., 2014).

#### ***Triclisia subcordata* Oliv. – Menispermaceae**

*T. subcordata* is a woody twine with broad-veined and reticulate leaves (Irvine, 1961). A slender woody liane of lowland rain-forest, recorded from Guinea to Nigeria and Angola. The stems are used as a tie. The plant contains alkaloids and is used to treat oedema, anaemia, diarrhoea, and joint pains (Burkill, 1985). It contains bisbenzylisoquinoline group of alkaloids, namely, phacanthine, tricordatine, pancholine, tetrandrine, and cocsuline. The tetrandrine has antitumor action (Oliver-Bever, 1986). The fruit is used for diabetes and obesity (Gill, 1992). Abo et al. (2011) reported strong presence of alkaloids in the root, traces of tannins and saponins; cardenolides and anthraquinones were absent. The antimicrobial potential of the roots (used to treat acute urinogenital infections and infertility) was tested against typed strains and clinical isolates of various pathogenic bacteria (Abo et al., 2011). The anti-ulcerogenic and muscle-relaxant effects in rats have been reported (Asuzu and Anaga, 1995).

#### ***Xylopiya aethiopic* (Dunal.) A. Rich – Annonaceae**

*X. aethiopic* is a deciduous tree of 20 m high or more with a clear straight bole (75 cm girth). It is commonly known as Negro pepper. It is widespread in Senegal, Nigeria, and East Africa. The fruit has value in the treatment of respiratory ailments: cough, asthma and bronchio-pneumonia. As a woman's remedy, it is taken to

encourage fertility and safe child delivery, also as postpartum tonic and for the treatment of amenorrhoea. Furthermore, the fruit is used to treat stomach-ache, dysentery, skin infections, neuralgia, and biliousness. It is used as purgative, anthelmintic, and anticonvulsant. The fruit is used as condiment in food. The root decoction is used as mouthwash for toothache. The powdered root is used as a dressing for sores and in local treatment of cancer. The seeds contain reberosides, avocean, resins, and essential oils (Oliver, 1960; Burkill, 1985; Gill, 1992). Phytochemical screening of *Xylopiya aethiopic* fruits indicated the strong presence of flavonoids, tannins; steroids, cardiac glycosides were moderately present; saponin and phenols slightly present, while alkaloids were absent. The nutritional value of the fruits has been evaluated by Abolaji et al. (2007). A comparative study of the stem bark and root of *X. aethiopic* showed the presence of alkaloids, saponins, flavonoids, tannins, terpenoids, steroids, cardiac glycosides, but not anthraquinones (Ekpo et al., 2012). An alkaloid (Anonacaine) obtained from *X. aethiopic* is known to have antipyretic and to relieve pain (Ekpo et al., 2012). Monoterpenes and sesquiterpenes have been isolated from the plant (Iwu, 1999). Preliminary phytochemical screening of the fruit extract (Ogbonnia et al., 2008) indicated positive results for alkaloids, polyphenols, and terpenoids. The monoterpene hydrocarbons were the main constituent of *X. aethiopic* essential oils and they exhibited significant antioxidant activity (Karioti et al., 2004). Xylopic acid and four other isolates from the fresh fruits displayed antimicrobial activity against *S. aureus*, *Bacillus subtilis*, *Escherichia coli* and *Candida albicans* (Boakye-Yiadom et al., 1977). Ilusanya et al. (2012) studied antimicrobial activity of the fruit extracts and its combinations with antibiotics against clinical bacterial pathogens. The *in vitro* study revealed 39.3% synergism and 57.1% antagonism. 3.6% of the treatment combinations were indifferent. The analgesic properties of the ethanol extract of its fruit and xylopic acid have been validated by Woode et al. (2012). The powdered fruits together with *Piper guineense* with small quantity of potash soaked in alcohol is taken to suppress fibroid in the uterus and facilitate conception (Gbadamosi and Otodo, 2014). Fleischer et al. (2003) reported the anti-inflammatory, antimicrobial, and anti-tumour activities of the plant.

#### **CONCLUSION**

In view of the reported adverse effects of orthodox anticancer drugs and the confirmed efficacy of medicinal plants, there is need to continuously search for plant-derived anticancer agents. The anticancer action of 6 out of 20 plants reviewed in this study has been scientifically validated. The plants with anticancer potential are: *A. ascalonicum*, *C. portoricensis*, *K. ivorensis*, *L. alata*, *P. zeylanica*, and *X. aethiopic*. Some of the plants also provide additional therapeutic value when consumed

as food especially *A. ascalonicum*. This study could form the basis for future research on anti-cancer agents of the reported plants in related faculties, such as forestry, microbiology, chemistry, pharmacognosy, pharmacology and basic medical sciences. Also, of importance is the sustainable use of the plant due to their valuable therapeutic effect in breast cancer management and treatment.

### Conflict of Interests

The authors have not declared any conflict of interests.

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## Full Length Research Paper

## Antinociceptive and healing activity of the methanolic and hydroethanolic extracts of *Caulerpa taxifolia*

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This study aimed to evaluate the healing and analgesic action of methanolic extract and hydroalcoholic of *C. taxifolia*, and check the percentage of soluble proteins available in the extract of this vegetable. The collection of *C. taxifolia* occurred on the beach of Barra do Sirinhaém - PE, processed for testing. The animals used in the test were Swiss mice, and *Mus musculus* of species. For healing activity and histopathological analysis, albino rats *Rattus norvegicus* species, linnhagem Wistar were used. The protein content of the crude extract of *C. Taxifolia* has not yet been determined. The data revealed that the average displaying writhing in animal control group was 13.86. The standard group was 7.83; the group treated with hydroethanolic extract of *C. taxifolia* at a dose of 50 mg/kg was 8.83 and those treated with 100 mg/kg was 6.5. In the groups treated with the methanol extract of 100 mg/kg, the average value of writhing was 7.67, while 50 mg/kg resulted in 9.26 average value. It was shown that hydroethanolic and methanol extract led to early healing of wound with epithelialized keratinized tissue and re-epithelialization; involving the restructuring of the skin appendages, during treatment and in the absence of crust.

**Key words:** Healing, seaweed, protein, repair.

### INTRODUCTION

Wound healing is a process of repair that follows after injury of the skin and other soft tissues, and encompasses a complex series of interactions between different cell types, inflammatory mediators, and extracellular matrix. It is the phase of wound healing involving hemostasis,

inflammation, proliferation and remodeling; and each phase is different, although the process is continuous (Riella et al., 2012). Since the first occurs in the first hours (hemostasis), this process occurs in platelet activation and consequent aggregation, fibrin and coagulation

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cascade. In the second stage, which occurs in days, the inflammatory process is present, and there is the recruitment of neutrophils and macrophages, which among other things help to degrade the devitalized tissue; and macrophages stimulate the growth of new tissue (Irion et al., 2005). Treatment of wound closes as quickly as possible the lesion in order to obtain a functional and aesthetically satisfactory scar. Medicinal products obtained exclusively from raw materials of vegetable origin called herbs provide active ingredients with anti-inflammatory and wound healing applications (Michelin et al., 2005; Lima et al., 2006).

Among the products of dermatological interest, particular attention deserves the action incorporated into the topical dosage forms. This can in turn allow recovery of intact posterior skin to possible attacks. For the restoration of normal conditions, the healing process is very important. In this context, the migration of inflammatory cells in granulation tissue synthesis, deposition of collagen and proteoglycans and maturation of the scar, are associated with severe reshaping. Thus, the complementary medicine works as a tool for this treatment (Santos et al., 2002; Mendonça, 2006; Rocha et al., 2006).

Several medicines for tissue healing mostly originate in natural products (Segundo et al., 2007). These biomaterials consist of interactive elements that are able to establish adequate affinity with the surrounding tissue, without however inducing adverse response of the host (Ratner and Bryant, 2004). Among the biomaterials, polysaccharides stimulate the immune system *in vitro* and *in vivo* in order to facilitate the healing process (Diallo et al., 2001; Kweon et al., 2003; Senel and McClure, 2004; Vitorino Filho, 2011).

The diversity of Brazilian marine flora favors the discovery of pharmacological agents in the prevention and treatment of diseases (Rodrigues et al., 2019). Sulphated polysaccharides (PS), and soluble proteins are found in these agents, in large concentrations and with interesting biological properties (Rodrigues et al., 2009).

These compounds have structural complexity due to the many possibilities of monosaccharides and distribution of sulfate groups, which vary from species to species, and sometimes in different parts of the plant (Alves, 2000; Haroun-Bouhedja et al., 2000).

The presence of polysaccharide sulfates can promote change in biological activity, since it modifies the conformation of its chain; makes nonpolar substances in water-soluble and also promotes interactions with cationic proteins (Shanmugam and Mody, 2000; Liu et al., 2009).

Some PS present in green algae are covalently bound to proteins, being classified as proteoglycans (Aquino et al., 2005; Ropelatto et al., 2011).

This group of organisms, which belongs to the genus *Caulerpa*, appears to differ sterols on cholesterol chemical structure. The compounds are biologically important as hormones, vitamins and structural

components of biomembranes (Ghosh et al., 2004; Lee et al., 2004; Shevchenko et al., 2009). Phytochemical approach to *Caulerpa taxifolia* indicated the presence of secondary metabolites such as alkaloids, terpenes, sterols and saponins (Moura et al., 2012). The caulerpina isolated alkaloid *C. taxifolia* was active in enterocolitis study model for mice (Lima et al., 2014). For Kathiravan et al. (2014), species of this genus can produce Ag nanoparticles and these extracellularly (nanoparticles) are quite stable in solution, likely due to leveling proteins present in the extract. This study aimed to evaluate the healing and analgesic action of methanolic extract and hydroethanolic of *C. taxifolia*, and check the percentage of soluble proteins available in the extract of this vegetable.

## MATERIALS AND METHODS

### Collection of vegetable material

Marine macroalgae *C. taxifolia* was collected on the beach of Sirinhaém Bar, county Sirinhaém - PE. Then it was placed in plastic bags with seawater and transported to the Experimental Oncology Laboratory, UFPE, where it was washed in distilled water and dried in an oven at 25°C temperature. It was later weighed and crushed in blender (Arno®) for macerating. It was put in a glass container with 50% hidroetanólica solution (a first portion) and another portion of methanolic solution of 100%. After 7 days of soaking the material was placed in rotatory evaporator and stored until the day of the test. The performance of hydroethanolic and methanol extract were 11.5 and 8.8% respectively.

### Laboratory animals

The animals used in the test of writhings were Swiss mice of the *Mus musculus* species; they were males of approximately 60 days old. They weighed 25 to 30 g after birth. They were kept in light controlled conditions (12-hour light / dark cycle) and temperature of 22 ± 2°C in polypropylene cages, where they received specific food and water *ad libitum*. 12 h prior to the study, the animals were fasted.

For the activity of healing, the animals used were the albino rats of the species *Rattus norvegicus*, linnhagem Wistar, of 120 days; weighing between 180-200 g. They were kept in controlled lighting conditions (12 h light / dark cycle) and temperature of 22 ± 2°C in polypropylene cages, where they received specific food and water *ad libitum*. 12 h before the surgical procedures, the animals were fasted. The present study was approved by the research ethics committee in animals of the Federal University of Pernambuco, being registered under the protocol number 179/04.

### Nociceptive activity

The writhing test in mice was carried out according to Koster et al. (1959). The methanolic and hydroethanolic extracts of *C. taxifolia* were solubilized in dimethyl sulfoxide: Tween 80 (1: 1) 1% (v / v) in saline and administered orally 1 hour before the application of 0.6% acetic acid. The control group (group 1) received 0.3 ml / 30 g of dimethyl sulfoxide: Tween 80 (1: 1) 1% in saline orally (po). Indomethacin (10 mg/kg) was the reference drug administered



orally to mice in the positive control group (group 2). Groups 3 and 4 were administered doses of 50 and 100 mg/kg of hydroethanolic extract of *C. taxifolia* respectively; 50 and 100 mg/kg of methanolic extract of *C. taxifolia* were given to Groups 5 and 6, respectively; rat weight (n=10). One hour after treatment, 10 ml/kg of 0.6% acetic acid was administered intraperitoneally in each mouse and the number of writhings was counted within a range of 10 and 30 min after this procedure.

The percentage inhibition of writhing was calculated by the formula: % Inhibition =  $[(\text{NC control} - \text{NC treaty}) \div \text{NC control}] \times 100$  where: NC control: number of writhes in the control group; NC treaty: writhing number of the treated group.

### Getting cream

The cream for the treatment of animals used in the healing experiment was obtained by adding extracts and solubilization of the cream base, in GLOBO® manipulated manipulation pharmacy. Constituents of base cream are: Water, 34.5%; Glycerin, 6.0, 5.0% cetostearyl alcohol; 3.0% glyceryl monostearate; sodium lauryl sulfate ester, 1.5% (Batista et al., 2011).

### Healing test

For the healing test 60 animals were selected which were divided into 12 groups (n = 5), where three groups each were treated topically with methanolic extract of *C. taxifolia*; hydroethanolic extract of *C. taxifolia*, cream base, and Bepantol cream. During the treatment there was removal of scar tissue of one of the three groups at 7, 14 and 21 days.

### Histopathological evaluation

All samples were fixed in 10% formalin, embedded in paraffin, cut in 5 mm and stained with hematoxylin-eosin (HE). These sections were then examined under a light microscope to detect histological changes by a histopathologist who did not know the groups. Slides were scored for the presence of vascularisation, edema, and degrees of acute and chronic inflammation.

### Morphological analysis

The morphometric analysis was performed on histological sections stained by HE. Each slide was measured by a high-power field magnified 400x including the healing of the incision area; the average number of collagen bundles in each group was calculated.

### Protein soluble analysis

The Bradford method (1976) was employed to determine the protein content of the crude extract of *C. taxifolia*. The reagent was prepared by solubilizing 50 mg Coomassie in 25 mL of ethanol (95%), with further addition of 100 ml of phosphoric acid (85% w/v). The final concentrations (w/v) of the reagent was 0.01% Coomassie, 4.7% ethanol and 8.5% phosphoric acid. Standard albumin solutions were prepared in increasing concentrations of 1.0 to 0.1 mg/mL, from dilutions of the stock solution (5 mg/ml).

Vegetable processed samples were cut into pieces (5 mm) and 200 mg was weighed and homogenized in 10 ml of 80% ethanol. An aliquot of the crude extract was centrifuged for 5 min at 2,000 g; an aliquot of 3 ml of the supernatant was transferred to a test tube, and 6 ml of chloroform was added to it. This mixture was stirred continuously for two minutes gently and then left unstirred for

10 min. So, there were two phases (organic and aqueous). The aqueous fraction (colorless) was collected in an eppendorf and kept in freezer until the time of color development.

For color development, pipetted 200  $\mu\text{L}$  of standard solutions and sample extracts were added to 4 mL of the Coomassie brilliant blue reagent. The tubes were subjected to gentle agitation for 5 min at rest. Then the readings were performed in a spectrophotometer at a wavelength of 595 nm; the amounts of soluble protein content were expressed in terms of mg of soluble protein per gram of fresh plant tissue (Bradford, 1976).

The concentration of soluble proteins was calculated by the formula: Focuses =  $[(\text{White Abs} - \text{Abs sample}) \div \text{white Abs}] \times 100$  where: Abs blank: absorbance measured for white; Abs sample: absorbance measured for the samples.

### Statistical analysis

The test of writhing was considered significant for values  $*** p < 0.001$ , after analysis of variance (ANOVA) followed by Student Newman-Keuls test when compared to the control group.

## RESULTS

### Nociceptive activity

The average displaying writhing in animal control group was 13.86; the standard group average was 7.83. The group treated with hydroethanolic extract of *C. taxifolia* at a dose of 50 mg/kg had 8.83; the group treated with hydroethanolic extract of *C. taxifolia* at a dose of 100 mg/kg showed an average value of 6.5. The groups treated with methanolic extract of *C. taxifolia* at a dose of 100 mg/kg had an average value of 7.67 and the twisted group treated with methanolic extract of seaweed at a dose of 50 mg/kg had 9.26 contortions as mean value (Table 1).

The control group treated with 50 mg/kg hydroethanolic extract had 36.3% decrease in writhing. T100 mg/kg hydroethanolic extract reduced writhing by 53.1%. With the methanolic extract of 50 and 100 mg/kg, there was a reduction of 33.2 and 44.7% respectively.

### Soluble proteins

In the spectrophotometric quantification of octoplicata-samples as soluble protein present in extract of *C. taxifolia*, readings were done according to the formula described by Bradford (1976), which was expressed as the mean  $\pm$  standard error of the mean. The result was  $6.67 \pm 1.32 \mu\text{g} / \text{mg}$ .

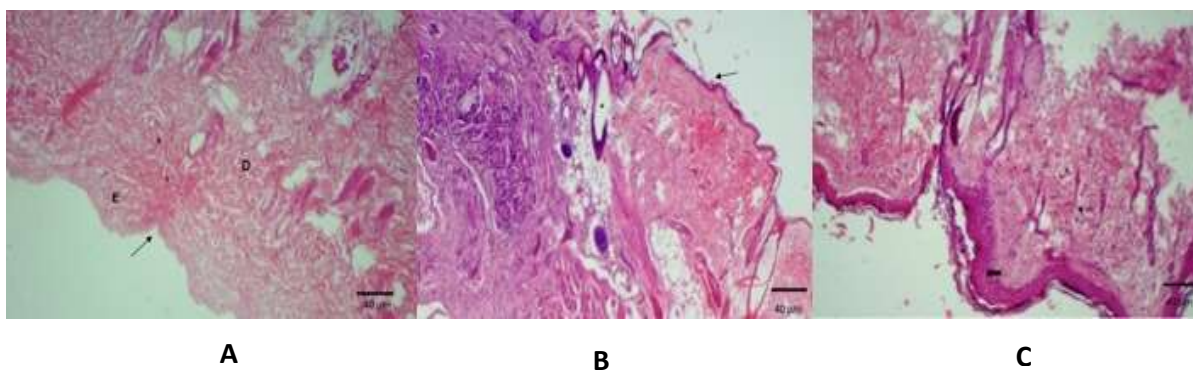
### Healing activity

It was shown that both the inorganic and organic extracts showed early wound healing with epithelialized keratinized tissue; with restructuring of the skin appendages, during the treatment and in the absence of crust (Figures 1 and

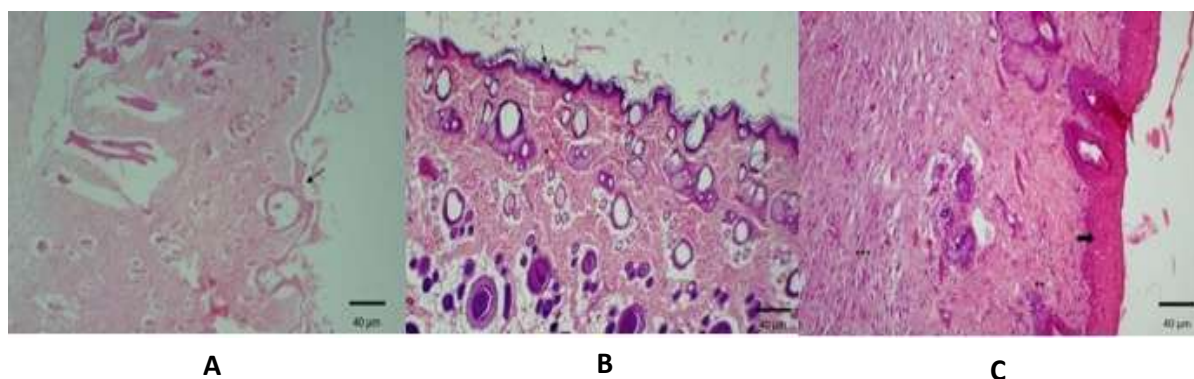
**Table 1.** Hydroethanolic and methanolic extract effect *C. taxifolia* on the writhing induced by acetic acid (n = 6).

Groups	Doses (mg/kg)	Number of contortions	Inhibition (%)
Control	Saline	13.86 ± 1.37	-
Methanolic extract	50	9.26±1.26***	33.18
	100	7.67± 1.12***	44.66
Hydroethanolic extract	50	8.83± 0.98***	36.29
	100	6.5 ± 0.85***	53.1
Indomethacin	10	7.83± 1.21***	43.5

\*\*\* p <0.001. Significant after analysis of variance (ANOVA) followed by Student Newman-Keuls test when compared to the control.



**Figure 1.** Photomicrography of skin healing animals. Treated group hydroethanolic extract for (A) 7, (B) 14 and (C) 21 days. Staining hematoxylin-eosin x40.



**Figure 2.** Photomicrograph of skin healing animals. Group treated with methanol extract for (A) 7, (B) 14 and (C) 21 days. Hematoxylin-eosin staining 40x.

2). However, the animals treated with the organic extract (21 days) showed inflammatory infiltrates (\*\*) and a significant number of fibroblasts (\*\*\*) when compared to treatments of 7 and 14 days.

## DISCUSSION

The data demonstrate that both extracts reduced writhing in mice with two doses tested, suggesting inhibition of

prostaglandin synthesis via cyclooxygenase, as well as indomethacin. Positive control test has the mechanism of inhibiting this enzyme (Duarte et al., 1992). The inhibition of contortions were quite significant at the tested doses, most apparent with the hydroethanolic extract of 100 mg/kg.

The test of writhings is a chemical model of nociception that is based on counting the contortions of the abdominal wall followed by the trunk torsion, and extension of the hind limbs, such as reflex response to peritoneal irritation and peritonitis produced by intraperitoneal injection of a solution of 0.9% acetic acid (Whittle, 1964). This test is sensitive to the evaluation of analgesic drugs; however, it can be seen as a general model, non-selective, for studies of antinociceptive drugs (Couto et al., 2011).

Para Julius and Basbaum (2001) sprouts coming from the dissociation of acetic acid can directly activate the nonselective cation channels located in primary afferent pathways. The local irritation produced by intraperitoneal injection of acetic acid causes the release of a variety of mediators such as substance P, bradykinin, prostaglandins, as well as the pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF- $\alpha$  (Pinheiro et al., 2011). Verma et al. (2005) comment that this method is associated with the release of prostanoids, in general, high levels of PGE2 and PGF2a and lipoxygenase products in peritoneal fluid.

The extracts of *C. taxifolia* (hydroethanolic and methanol) exhibited antinociceptive activity in the model induced by acetic acid. The responses were significant at both doses of extract, and the percentage of inhibition increased with increasing dose. This can be related with the synthesis of prostaglandins via cyclooxygenase as well as indomethacin (Sousa, et al., 2009).

The substance P and bradykinin are involved in the first phase, while histamine, serotonin, prostaglandins and bradykinin participate in the second phase of the response (Shibata et al., 1989). Morrow and Roberts II (2001) and Costa-and-Sousa (2010) indicate that the test of writhings involves anti-inflammatory mechanisms. In the process of tissue repair, under physiological conditions, fibroblasts are encouraged to migrate to the area of injury and produce collagen fibers to effect this process (Honorio-França et al., 2008; Mendonça; Coutinho Netto, 2009; Dias, 2012). In skin lesions, it is possible to assess the stage of tissue damage by histological analysis (qualitative and quantitative) of the main features that show the evolution of this process, such as the number of inflammatory cells, fibroblasts, and of new blood vessels formed by angiogenesis process (Batista et al., 2010; Oliveira et al., 2010).

Moreover, macrophages stimulate the growth of new tissue, as observed in animals in the 7th day, as well as the presence of small collagen fibers. The third stage of healing that occurs around days to weeks, was more intensified and there was continuous reepithelization of

the formation of granulation tissue. This fact can be seen in animals related to the 14th day. The presence of macrophages at this stage stimulates production of fibroblasts and deposition of loose connective tissue; whereas the collagen produces fibroblast migration. It was noticed that in the group of animals on the 21st day, the third stage was still present. This is explained by the depth of the lesion, which can be a limiting factor for the evolution of healing (Irion, 2005).

The extracts appear to have acted in the healing of treated animals promoting epithelization. According to Modolin and Bevilacqua (1985), at the end of the proliferative phase is re-epithelization of the lesion, which is controlled by chalone, a glycoprotein complex that stimulates epithelial mitotic activity.

Rubin and Farber (2002), Stevens and Lowe (2002) say proliferative phase lasts for 12 to 14 days, and is characterized by repairing the connective tissue with granulation tissue formation and consecutive repitelização. The repair process begins with inflammation and around 24 h after injury there is no resolution; fibroblasts and vascular endothelial cells initiate proliferation forming scar tissue, that is, granulation. It is histologically characterized as vasculogenesis and has increased numbers of fibroblasts.

Agnol (2008) further notes that in the repair process, by the second and third day after injury, the collagen-producing fibroblasts are recruited from the shores of injury and induce protein synthesis by fibroplasia. Consequently, the fibrinogen present in the inflammatory exudate turns into fibrin, which will serve for adhesion and proliferation of fibroblasts, which secrete scar tissue.

Therefore, the silver nanoparticles found in *Caulerpa taxifolia* possibly leveraging (in conjunction with) their potential antibiotics may be responsible for the healing effect since, with the control of the local microbiota developed, the mechanism for healing does not suffer interference.

## Conflicts of Interests

The authors have not declared any conflict of interest.

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