

**Review Article****A Review on Herbal Plants with Anti-Tumour Properties**David Arome^{1*}, Agbafor Amarachi²¹Department of Science Laboratory Technology, University of Jos, Nigeria²Department of Biomedicine, University of Portsmouth, United Kingdom

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ABSTRACT

Despite the advancement in molecular biology and state of the art facilities, a cure for cancer is unavailable. The significant unwanted side effects associated with the available conventional treatment approach has triggered considerable interest in the exploration of herbal remedies. Presently, Strategies are focused on the corporation of herbal medicine in the treatment of cancer. Herbal medicines have contributed significantly in the development of modern day pharmaceutical products with novel structures, better safety and efficacy profiles. About 28% of modern pharmaceutical products are obtained from herbal plants. The objective of the review was to highlight some of the treatment options: Conventional, herbal and unveiling new treatment approach employed in management of cancer disease, in view of the numerous adverse effects associated with the use of conventional anti-cancers drugs.

Keywords: Anti-cancer drugs; conventional approach; herbal medicine; treatment options

INTRODUCTION

Cancer remains as one of the key global health care challenges claiming the lives of millions every year. The prevalence of cancer is on a steady increase with an estimated case of 7.6 million deaths recorded in 2008 [1], however, this figure is predicted to double in 2030 [2]. Cancer is a multi-factorial systemic disease [3], characterized by abnormal and unrestrained growth of cells in body organs or tissues. It is usually accompanied by

explicit defined features such as uncontrollable, proliferation, dedifferentiation and loss of function, invasiveness and metastases [4], which distinguish them from the normal body cells. They are no précised aetiology of cancer but scientists have attributed the possible cause to two main factors: Genetic diversity and environmental factors [5]. Carcinogenic agents associated with environment factors are: X-rays, UV light, viruses, tobacco products, pollutants, and many other chemicals [5]. Despite the major advancement in molecular

biology and state of the art facilities, a cure for cancer is still unavailable. The significant unwanted side effects associated with the available conventional treatment approach has triggered considerable interest in the exploration of herbal remedies. Presently, Strategies are focused on the incorporation of herbal medicine in stemming the scourge of cancer disease [6]. Scientific investigations over the years have indicated herbal preparations to be effective against wide range of diseases with little or no side effects associated with their use [7].

Herbal medicines have contributed significantly in the development of modern day pharmaceutical products with novel structures and better safety and efficacy profiles [8]. About 28% of modern pharmaceutical products are obtained from herbal plants [9]. Extracts from herbal plants are regarded as chemical libraries of structurally diverse compounds, therefore constituting a promising approach in drug development and discovery [10]. Herbal plants have unique features that differentiate them from other chemical agents; a single plant may contain broad spectrum of bioactive ingredients [11]. Herbal plants have less adverse effects profile and have proven to compete favourable in efficacy like their synthetic counterpart [12-14]. The objective of the review was to highlight some of the treatment options: Conventional, herbal and unveiling new treatment approach employed in management of cancer disease.

Cancer promoting agents

Cancer promoting agent for example virus, bacteria and parasitic (infectious microbes) altered the genetic permutation that regulate the working mechanism of the cell signal that control cell

division and growth. Infectious microbes can trigger cancer through the following ways:

1. Alteration of the genetic structure: Virus depends solely on its host to replicate. On entering the body interact directly with the DNA. This interaction altered the genetic configuration, which lead to the activation of cancer promoting genes, or through inactivation of the cancer suppressor genes [15].
2. Chronic inflammation: Infectious microbes can trigger the body immune system to initiate cascade of activities that can lead to inflammation. Persistent inflammation can as well triggered abnormal rapid division of the cell than normal rate, which increase the likelihood of continue genetic mutation which can lead to cancer [15].
3. Reduced immune mechanism: Infectious microbes can reduce the effectiveness of the body defence mechanism in fighting and recognising cancer promoting agents [15].

Common viruses that promote cancer

Oncogenic viruses infect normal cells and cause alterations in the cell's genetic material. These genetic alterations can cause specific types of malignant and benign cancer [16.] Oncogenic virus can affect either the DNA or RNA. The viruses that commonly promote cancer are itemized below:

1. Human papillomavirus (genital carcinomas)
2. Hepatitis B (liver carcinoma)
3. Epstein-Barr virus (Burkitt's lymphoma and nasopharyngeal carcinoma)
4. Human T-cell leukemia
5. Virus (T-cell lymphoma)
6. Herpes virus called KSHV (Kaposi's sarcoma and some B cell lymphomas) [16]

Table 1. Differences between normal and cancer cells [19]

Normal cell	Cancer cell
Normal cell divide in an orderly fashion	Cancer cell violates the cell signal that control the normal division of the cell, thereby dividing incorrectly and spread to a wide area
Function at a normal metabolic rate and reproduce themselves in a regulated pattern	Cancer cell overactive or overproduce themselves, thereby requiring more nutrients
Obtained most of it energy (about 70%) through the Krebs's cycle mechanism	Exhibited a defective Krebs's cycle with little energy derive from this mechanism
Possesses an inbuilt blood vessels	Lack inbuilt blood vessels system (by basically through angiogenesis)
Derive most of its energy using oxygen	Derive most of its energy in the absence of oxygen
Have DNA in their genes and chromosomes that function normally	Develop an abnormal DNA or genes structure

Pathogenesis of cancer

The pathogenesis of cancer is a complex one. The three main changes that characterized the pathogenesis of cancer are;

1. The activation of proto-oncogenes to oncogenes: Proto-oncogenes are genes that are found in every cell. Mutation of the oncogenes resulting from damage and alteration by exposure to carcinogens can cause a cell to grow unrestrainedly and infiltrate and destroy normal tissues [17].
2. The inactivation of tumour suppressor genes: These genes normally inhibit cell division and prevent survival of cells that have damaged DNA. Mutation of the suppressor genes as a result of exposure to carcinogens altered the control mechanism of the genes that have the ability to suppress malignant change. The loss of function of tumour suppressor gene forms the very basis of pathogenesis of cancer [17]. Mutations of these two principle genes; Oncogenes and tumour suppressors accelerate and prevent the normal inhibition of cell growth.

3. Mutation of the DNA repair genes: DNA genes repair and maintain the structural integrity of the chromosomes. Exposure of these genes to environmental factors like UV light, radiation can lead to their damage as well as error in the expression of DNA can cause mutation.

Tumour biology

“Misbehaving” cancer cells exist as autonomy cells without following the normal rules of cell growth and division resulting to tumour. Tumours grow in a series of multistep

1. Hyperplasia
2. Dysplasia
3. Anaplastic

The last step occurs when the cells in the tumour metastasize, which means that they can invade surrounding tissue, including the bloodstream, and spread to other locations. This is the most serious type of tumour, but not all tumours progress to this point. Non-invasive tumours are said to be benign [18].

Classification of cancer

1. Carcinomas: Carcinomas are cancer that stem from cells covering the surface layer or lining membrane of organ. Common examples of carcinomas are: breast, lung, skin rectum.
2. Sarcomas. This category of cancer is associated with connective tissues. Examples of sarcoma: fibrosarcoma, chondrosarcoma.
3. Leukemia: This cancer type occurs as a result of disorganization and rapid proliferation of the blood forming tissue within the bone marrow and often accumulates in the blood stream.
4. Lymphoma and myelomas. This type of cancer originates from the immune system.
5. Adenomas. This type of cancer stem from the thyroid, pituitary, adrenal and other glandular glands [19].

Tumour markers

Tumour marker also known as biomarker is a glycoprotein that is altered quantitatively or qualitatively in precancerous or cancerous state,

this changes can be detected by bioassay [20]. The alteration or changes in the biomarker can be as a result of tumour itself or as a result of response to tumour cells by the surrounding normal tissues [20]. Tumour markers are mostly protein, genes, enzymes, oncogenes, antigens measured by appropriate bioassay.

Clinical application of biomarkers

1. Screening and early detection of cancer
2. Prognosis and prediction of therapeutic response to treatment
3. Monitoring of disease and recurrence
4. Screening of high-risk individuals
5. Diagnostic confirmation
6. Determination of the present of cancer^[21]

Increase in biomarkers do not necessary indicates the present of cancer. Biomarkers increase in some disease conditions other than cancer, varying over time, and in some cases may remain low until cancer advanced.

Table 2. Different cancer types and their test modalities

Cancer type	Biomarkers	Found in	Test modality	References
Prostate	PAP	Serum	ICMA,	22,23
	PSA	Blood	ICMA	
	E-cadherin	Tissue	IHC	
	P53	Tissue	IHC	
	Epidermal growth receptor	specimen	IHC	
Breast cancer	CA27.29	Serum protein	ICMA	24,25
	BRCA (BRCA1 or BRCA2)	Blood	PCR	
	CA15-3	Serum	ICMA	
	CEA	Serum	ICMA	
	HER2/neu	Tissue	ICH, EIA	
	MIB-1	specimen	IHC	
		Tissue		

Lung	CEA	Serum	ICMA,	24, 26
	ACTH	Plasma	ICMA	
	AFP	Serum	ICMA	
	CA27.29	Serum	ICMA	
Kidney	Bladder tumour antigen	Tissue	EIA,	24
			Cytology	
Ovarian	BHCG	Tissue	ICMA	27,28, 29
	CA-125	Tissue	MEIA	
	BRCA	Whole blood	PCR	
	CEA	Serum	ICMA	
	HER2/neu	Tumour tissue	IHC, FISH	
Cervical	CA125	Serum	ICMA	24, 30
	HPV	Pap smear	DNA	
	EGFR	Tissue specimen	IHC	
Colonrectal	AFP	Serum	ICMA	24
	CA125	Serum	EIA	
	CEA	Serum	ICMA	
	Faecal gloobin	Blood	IHC	
	Lipid associated sialic acid	Blood	Spectophotom	
	Colaris AP (APC, FAP)	Blood	PCR	
Bladder	BTA	Urine	EIA	24
	Immunocyt	Urine	ICC	
	Nuclear matrnx protein	Urine	EIA	
	P53 tomour suppressor	Tissue	IHC	
Liver	AFP	Serum protein	ICMA	24
	BHCG	Serum	ICMA	
	CA19.9	Serum	EIA	
	CA27.29	Serum protein	ICMA	
Pancreatic	AFP	Serum	ICMA	24,31
	BHCG	Serum	ICMA	
	CA125	Serum	ICMA	
	CA19-19	Serum	EIA	
	CEA	Serum	ICMA	
Leukemia	Cd 33	Blood	Cytometry	24, 32
	FLT3	Blood	PCR	
	BCR/ABL	Bone marrow	PCR, FISH	
Lymphoma	B-cell rearrangement	Whole blood	PCR	24
	Cd 20	Blood	Cytometry	
	Beta2 microglobin	Serum	ICMA	

	Cyclin d-1		Blood, tissue	FISH	
Melanoma	Tumour antigen 90 immune complex		Serum	PCR	33
	Melaris		Blood	EIA	
Endometrial	Colaris (MLH1, MSH2)		Blood	PCR	24,33
Thyroid	ACTH		Plasma		24
	Calcitonin		Serum		
	Thyroglobulin		Serum		

These tumour markers are used in combination with biopsy to give a better picture of the clinical relevance of the cancer

Table 3. Acronyms for biomarkers and diagnostic test modalities [24]

CEA	Carcinoembryonic antigen
BHCG	Beta human chorionic gonadotrophin
ACTH	Andrino-corticothyroid hormone
AFP	Alpha-fetoprotein
EGFR	Epidermal growth factor receptor
BTA	Bladder tumour antigen
PSA	Prostate specific antigen
PAP	Prostatic acid phosphatase
PCR	Polymerize chain reaction
HPV	Human papillovirus
ICMA	Immunochemiluminometric assay
EIA	Enzymes immunoassay
FISH	Fluorescence in-situ hybridization
ICC	Immunocytochemistry
IHC	Immunochemistry
DNA	Deoxyribonucleic acid

New prospect of diagnostic test modalities

Genomics

The science of genomics is basically the study of structural changes in DNA or mutation of the DNA. DNA is the molecule that control functional mechanism of all cells [21]. Alteration to the DNA permutation as a result of exposure to carcinogens can be checked in urine, serum, stool urine and tissues and this may be useful modality to scientist in the early detection of cancer and effectiveness of therapy [21]. Looking at the patterns of changes is likely to prove more useful than looking for single DNA changes [32].

Proteomics

Unlike genomics, proteomics is the study of protein shape, function, and patterns of expression. Proteomic knowledge may serve as a very important screening tool for cancers. With this new testing modality thousands of protein can be viewed at a time. This helps in the assessment of the protein levels associated with certain type of cancer [21].

These new testing prospect is still in the early stages of development. Very few of these methods are in routine use.

Table 4. Classes of anti-cancer drugs and their mechanism of reactions [4, 34]

Classes of anti-cancer	Mechanism of reaction
Alkylating agent	Disturb the integrity and function of DNA thereby altering the synthesis of DNA and cell division
Anti-metabolites	They act on intermediary metabolic pathway of proliferating cells, thereby preventing DNA and RNA synthesis
Natural products tic (Anti-mitotic)	Act by binding to specific β -tubulin and block its ability to polymerize with α -tubulin into microtubules
Anti-biotic	Inhibit rapid proliferation of normal cell and cancer origin, thereby making a single strand to break in DNA, possibly through a free radicle intermediate or as result of the action of lopoisomearse II
Hormones	Suppress hormone secretion or antagonise hormone
Miscellaneous agents	Inhibit the enzymes ribonucleoside diphose reductase which catalyzes the reductive conversion of ribonucleoside to deoxyribonucleoside

General toxicological profile of anticancer drugs:

- Bone marrow toxicity
- Gastrointestinal tract toxicity
- Hair follicle toxicity
- Neurotoxicity
- Renal toxicity
- Ototocity
- Cardiomyopathy

New treatment options

- Chemo-immunotherapy:** This technique involves the direct attachment of chemotherapeutic agents with anti-bodies. The anti-bodies then delivery the agent directly into the cancer cells without harming the normal body cells. The chemotherapeutic agents target the cancer cells through the anti-bodies as a conveying vehicle [17].

- b. **Radio-immunotherapy:** This new technique involves the cooperation of antibodies to radioactive atoms (particles), specifically, targeting the deadly radiation. Side effects; destruction of bone marrow [17].
- c. **Gene therapy:** The rationale behind the used of this new technique is to replace the damaged genes with a new copy of a working gene. The application of gene based therapy also focus on targeting the damaging cancer cell of DNA to undergo self-induced apoptosis [18].

Table 5. Herbal remedies used in the management of cancer

Plant family	Part used	Phytochemical constituents	Uses	Models	References
<i>Persea americana</i> (Lauraceae)	Stem, root and bark	Saponnins, tannins, cardiac glycosides, flavonoids, terpenes, phlobatanis	Treatment of tumour, trypanocidal activity.	Bench top bioassay: Anti-proliferative model (using <i>Sorghum bicolor</i> seeds), Cytotoxic model; <i>Raniceps ranninus</i>	35-38
<i>Piper crocatum</i> Ruiz and pav	Leaves	Saponins, tannins, terpenes	Breast cancer treatment	Sub-G1 apoptosis assay and flow Cytometry, cell viability assay, Structural analysis and DAPI staining, Immunoblotting.	39-40
<i>Zingiber zerumbet</i> (Zingiberaceae)	Rhizome	Zerumbone	Constipation, stomachache, fever	Cell proliferation assay,	41-44
<i>Magnolia grandiflora</i> Linn. (Magnoliaceae)	Bark	--	antineoplastic and antioxidants properties, skin tumour	Invivo tumour growth inhibition, MTT assay	45-50
<i>Calea pinnatifida</i>	Aerial	--	treatment of stomach ache, giardiasis, and amoebiasis, antiinflammatory,	In vitro anticancer activity assay, In vivo assay – Ehrlich tumor,	51-55

			antiplasmodial, antileishmanial, acaricidal, antifungal, antimicrobial, and Cytotoxic	Ehrlich ascites assay, Ehrlich solid assay	
<i>Cymbopogon citratus</i>	Leave and root	Saponins, flavonoids, cardiac glycosides,	Pain and inflammation, tumour, diabetes,	Anti-proliferative model,	56-57
<i>Astrodaucus persicus</i> (Apiaceae)	Root	--	Management of cancer related diseases	In vitro cytotoxicity assay, MTT assay	58-60
<i>Juglans regia L</i>	Root bark	α -tocopherol, γ -tocopheral, ellagic acid	Management of prostate cancer, reducing apoptosis, inhibit angiogenesis, reduction of low density	Cell viability assay, cell proliferation assay and determination of IC ₅₀	61-65
<i>Scrophularia oxysepala</i>	Leaf and stem	iridoids, ridoid glycosides, phenylpropanoid glycosides, phenylethanoid glycosides, resin glycosides, sugar esters, flavonoids, terpenoids and saponins	erythema, eczema, wounds, inflammation of skin, mouth dryness, sore throat, ulcers, goiter, tonsillitis, furunculosis, constipation, aching bones, abscesses, fistulas and cancer.	MTT assay, trypan blue assay, TUNEL assay for detection of DNA fragmentation	66-76
<i>Kedrostis Foetidissima</i> (Curcubitaceae)	Leaf and stem	--	Treatment of tumour	MTT assay, flow cytometry	77-78
<i>Ononis hirta</i>	Aerial part	Alkaloids, terpenoids, flavonoids	Possesses anti-tumour property, pain.	Anti-proliferative assay	79-82
<i>Verbascum</i>	Flower	Terpenoids,	Used folkloric	MTT assay	79-82

<i>sinaiticum</i>		flavonoids	medicine in the management of tumour		
<i>Anona muricata</i>	Seed	Alkaloids, flavonoids, tannins, saponins, muricine	Used in the treatment of influenza, desentery, tumour, cancer, inflammation, as insect repellent	Cytotoxicity assay	83-85
<i>Andrographis paniculata</i>	Leaf	Alkaloids, saponins	Possesses anti-viral, anti-biotic activity anti-tumour, immune-stimulant	Cytotoxicity assay	83-85
<i>Garcinia kola</i>	Leaf	Alkaloids flavonoids, saponins	Used as an anti-ulcer property, anti-pyretic effect, anti-inflammatory property	MTT assay	83-85
<i>Cuscuta Reflexa Roxb (Cuscutaceae)</i>	Whole plants	kaempferol-3-O-glucoside, astragallicin, myrecetin, benzopyrones, glucopyranosides, propenamide, flavonols, quercetin and quercetin-3-O-glucoside, β -sitosterol, and bergenin	impotence, premature ejaculation, sperm leakage, frequent urination, ringing in the ears, lower back pain, sore knees, leucorrhoea, dry eyes, blurred vision, and tired eyes.	Cell viability assay	86-91
<i>Abelmoschus moschatus</i>	Leaf and seed	Phenols, flavonols, quercetin	Treatment of intestinal complications, ophthalmic, aphrodisiac	Anti-proliferative assay	92-93
<i>Jatropha curcus (Euphorbiaceae) Linn</i>	Leaf	Flavonoids, phenols, saponins,	Management of pain and inflammation,	Cytotoxic effect by brine shrimp assay, anti-	94-98

<i>Kaempferia galangal</i> (Zingiberaceae) Linn	Tuber	Alkaloids, tannins, flavonoids, saponins	tumour Used in the treatment of constipation, intestinal infection, cancer	tumour activity by agrobacterium induced tumours in potato disc Anti-mitotic screening by onion root method, Cytotoxic effect by brine shrimp assay	95-97
<i>Lens culinaris</i> (Fabaceae)	Leaf	Flavonoids, tannins, saponins, alkaloids	Treatment of constipation, intestinal, ulcer tumour problem	Anti-tumour screening by assessment of tumour related body weight in DLA tumour induced mice, Cytotoxic effect by brine shrimp assay, Cytotoxic effect by brine shrimp assay	67, 72

CONCLUSION

The significant unwanted side effects associated with the available conventional treatment approach has triggered considerable interest in the exploration of herbal remedies. Herbal plants have less adverse effects profile and have proven to compete favourable in efficacy like their synthetic counterpart. In a nutshell, the application of herbal medicine has proven to be effective and can as well serve as an alternative option in the management of cancer.

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