



Potential of Central, Eastern and Western Africa Medicinal Plants for Cancer Therapy: Spotlight on Resistant Cells and Molecular Targets

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Cancer remains a major health hurdle worldwide and has moved from the third leading cause of death in the year 1990 to second place after cardiovascular disease since 2013. Chemotherapy is one of the most widely used treatment modes; however, its efficiency is limited due to the resistance of cancer cells to cytotoxic agents. The present overview deals with the potential of the flora of Central, Eastern and Western African (CEWA) regions as resource for anticancer drug discovery. It also reviews the molecular targets of phytochemicals of these plants such as ABC transporters, namely P-glycoprotein (P-gp), multi drug-resistance-related proteins (MRPs), breast cancer resistance protein (BCRP, ABCG2) as well as the epidermal growth factor receptor (EGFR/ErbB-1/HER1), human tumor suppressor protein p53, caspases, mitochondria, angiogenesis, and components of MAP kinase signaling pathways. Plants with the ability to preferentially kills resistant cancer cells were also reported. Data compiled in the present document were retrieved from scientific websites such as PubMed, Scopus, Sciencedirect, Web-of-Science, and Scholar Google. In summary, plant extracts from CEWA and isolated compounds thereof exert cytotoxic effects by several modes of action including caspases activation, alteration of mitochondrial membrane potential (MMP), induction of reactive oxygen species (ROS) in cancer cells and inhibition of angiogenesis. Ten strongest cytotoxic plants from CEWA recorded following *in vitro* screening assays are: *Beilschmiedia acuta* Kosterm, *Echinops giganteus* var. lelyi (C. D. Adams) A. Rich., *Erythrina sigmoidea* Hua (Fabaceae), *Imperata cylindrical* Beauv. var. koenigii Durand et Schinz, *Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A., *Piper capense* L.f., *Polyscias fulva* (Hiern) Harms., *Uapaca togoensis* Pax., *Vepris soyauxii* Engl. and *Xylopi aethiopica* (Dunal) A. Rich. Prominent antiproliferative compounds include: isoquinoline alkaloid isotetrandrine (**51**), two benzophenones: guttiferone E (**26**) and isoxanthochymol (**30**), the isoflavonoid 6 α -hydroxyphaseollidin (**9**), the naphthyl butenone guieranone A (**25**), two naphthoquinones: 2-acetylfuro-1,4-naphthoquinone (**4**) and plumbagin (**37**) and xanthone V₁ (**46**). However, only few research activities in the African continent focus on cytotoxic drug discovery from botanicals. The present review is expected to stimulate further scientific efforts to better valorize the African flora.

Keywords: Africa, cancer, plants, phytochemicals, molecular targets, resistance

INTRODUCTION

Cancer is a term for a series of malign diseases characterized by abnormal cell proliferation, leading to invasion and metastasis, the ultimate causes of deaths by cancer. The burden of neoplastic diseases affects the entire world population. Over the past two decades, there has been a slight improvement in cancer statistics due to diagnostic and therapeutic progresses and a better understanding of tumor biology (Siegel et al., 2014). However, cancer remains associated with very high mortality rates, which indicate still existing difficulties of effective treatment. Chemotherapy is one of the most widely used modes of anti-cancer therapy. However, the development of resistance of cancer cells to cytotoxic agents represents a main factor, which is responsible for the non-satisfactory treatment outcomes associated with malignant diseases (Singh and Settleman, 2010). In fact, most types of cancer cells reveal variable degrees of resistance to antineoplastic agents (Luqmani, 2005). In 2008, men in Africa had more than double of the rate of world liver cancer cases, whilst women had the highest incidence of cervical cancer of the world. Medicinal plants have long been used to fight against cancer. Several natural products isolated from medicinal plants

including: terpenoids, phenolics, and alkaloids play an important role in cancer treatment (Kaur et al., 2011). More than 3,000 plants worldwide have been reported to exert cytotoxicity toward cancer cells (Graham et al., 2000; Solowey et al., 2014). About 80% of the rural African population almost exclusively uses traditional medicine for its primary health care needs (Farnsworth et al., 1985). For cultural and economic reasons, medicinal plants constitute the major part of traditional medicine. In the recent years, numerous African medicinal plants have been screened for their cytotoxic potential. This review deals with plants and derived molecules from Central, Eastern and Western Africa (CEWA) as potential resource for cancer chemotherapy with emphasis on their molecular targets. Countries of Central Africa include: Cameroon, Gabon, Equatorial Guinea, Central African Republic, Congo, Democratic Republic of Congo, São Tomé and Príncipe, Chad, Angola. East Africa comprises of Kenya, Uganda, Tanzania, Rwanda, Burundi, Sudan, Eritrea, Djibouti, Ethiopia, Somalia, Seychelles, Comoros, Mauritius Island, Madagascar, Mozambique, and Malawi. Western African countries include Benin, Burkina Faso, Ivory Coast, Gambia, Ghana, Guinea, Guinea-Bissau, Cape Verde, Nigeria, Mali, Mauritania, Niger, Liberia, Senegal, Sierra Leone, and Togo. Hence, the medicinal plants of CEWA described in the present review cover a considerable portion of the African continent.

Abbreviations: 4E-BP1, 4E-binding protein 1; ABC transporters, ATP binding cassette transporters; Akt, protein kinase B; AMPK, AMP-activated protein kinase; Apaf-1, apoptotic peptidase activating factor 1; AR, androgen receptor; ARE, antioxidant response element; ATM/Chk1, ataxia-telangiectasia-mutated/check point kinase-1; BAD, Bcl-2-associated agonist of cell death; Bax, Bcl-2-associated X protein; BCRP, breast cancer resistance protein; BRCA, breast cancer; BTG3, B-cell translocation gene 3; C/EBP α , CAAT-enhancer binding protein α ; CCL2, CC motif ligand 2; Cdc2, cyclin-dependent kinase 1; Cdc25a, cell division cycle 25 homolog A; cIAP, cellular inhibitor of apoptosis protein; COX, cyclooxygenase; CXCL, chemokine (C-X-C motif) ligand; CXCR4, chemokine (C-X-C motif) receptor 4; CYP1A1, cytochrome P450 1A1; DR5, death receptor 5; EGFR, epidermal growth factor receptor; EMMPRIN, extracellular matrix metalloproteinase inducer; ErbB2, Receptor tyrosine-protein kinase; ERK, extracellular signal-regulated kinase; ER- α , - β , estrogen receptor - α , - β ; Fas, Fatty acid synthase; FoxM1, forkhead box M1; FOXO, forkhead transcription-factor O; G3BP1, GTPaseactivating protein (SH3 domain) binding protein 1; GDF15, growth differentiation factor 15; Gli1, glioma-associated oncogene 1; GST, glutathione transferase; HIF-1 α , hypoxia inducible factor 1, alpha; HMG-CoA, hydroxy-methylglutaryl-coenzyme A; Hsp70, heat shock 70 kDa protein; hSULT1A1, human simple phenol sulfotransferase; hSULT2A1, human dehydroepiandrosterone sulfotransferase; IDO, indole amine 2,3-dioxygenase; IGF-1R, insulin-like growth factor -1 receptor; IGF1BP, insulin-like growth factor binding protein; IGF, insulin-like growth factor; IKK, I κ beta kinase; IL, interleukin; IL-1RI, IL-1 receptor type I; iNOS, inducible nitric oxide synthase; JNK, c-Jun NH(2)-terminal kinase; MAPK, mitogen activated protein kinase; MDR, multi-drug resistance; MMP-2, -7, -9, matrix metalloproteinase-2, -7, -9; MMP, mitochondrial membrane potential; MRPs, multi drug resistance proteins; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor- κ B; Nrf2, nuclearfactor erythroid 2 related factor 2; PAK1, p21-activated protein kinase 1; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; PGE2, prostaglandin-E2; P-gp, P-glycoprotein; PHB, prohibitin; PI3K, phosphatidylinositol 3-kinase; Pin1, peptidyl prolyl cis/trans isomerase; PKC- α , - δ , protein kinase C - α , - δ ; PPAR γ , peroxisome proliferator-activated receptor-gamma; PTEN, phosphatase and tensin homolog; QR, quinone reductase; RAR- α , - β , retinoic acid receptor- α , - β ; RB, retinoblastoma; Skp2, S-phase kinase-associated protein 2; SphK1, sphingosine kinase 1; TGF β , Transforming growth factor- β ; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; UGT1A, uridine 5'-diphosphate-glucuronosyltransferase 1A; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; WIF-1, Wnt inhibitory factor-1; XIAP, X-linked inhibitor of apoptosis; ZEB1, zinc finger E-box binding homeobox 1.

OVERVIEW OF CANCER BURDEN IN AFRICA

Cancer moved from the third leading cause of death worldwide in 1990 to the second leading cause of death after cardiovascular disease since 2013, with more than 8 million deaths in 2013 (Murray and Lopez, 1997; Lozano et al., 2012). Although significant progress has been made in recent years in cancer prevention and treatment (Edwards et al., 2014; Allemani et al., 2015), the burden of cancer is increasing as a result of a growing and aging population worldwide, in addition to risk factors such as smoking, obesity and diet. To adequately allocate resources for prevention, screening, diagnosis, treatment and palliative care, and to monitor its effectiveness, there is an urgent need for timely information on the burden of cancer for each country. It is worth noting that in several African countries, the cancer burden still remains unclear in terms of reliable epidemiological data, though most practicing physicians recognize that the number of cases among patients visiting local health facilities continuously increases (Omosa et al., 2015). By 2020, 15 million new cancer cases are annually expected, 70% of which will be from developing countries. African countries will account for more than a million new cancer cases per year and have to cope with them despite few cancer care services (Vorobiof and Abratt, 2007). In Africa, about a third of cancer deaths are potentially preventable. In sub-Saharan Africa in 2002, more than half a million deaths from cancer were reported, with nearly 40% related to chronic infections and smoking (Vorobiof and Abratt, 2007). Due to the lack of basic resources and infrastructure, most Africans, including those in CEWA, do not have access to cancer screening, early diagnosis, appropriate treatment or palliative

care. For example, radiotherapy is available in only 21 of the 53 African countries, reaching less than 5% of the population, and consequently patients are deprived of life-saving treatment (Vorobiof and Abratt, 2007).

MOLECULAR TARGETS OF PHYTOCHEMICALS AND THEIR ROLE IN THE RESISTANCE OF TUMORS TO CYTOTOXIC DRUGS

The role of phytochemicals as cytotoxic agents against cancer cell lines has frequently been reported. Various plant molecules including nutraceuticals, such as allicin, apigenin, berberine, catechin gallate, celastrol, curcumin, epigallocatechin gallate, fisetin, flavopiridol, gambogic acid, genistein, plumbagin, quercetin, resveratrol, silibinin, taxol, etc. derived from spices, legumes, fruits, nuts, and vegetables have been shown to modulate inflammatory pathways and exert inhibitory effects against tumor cells (Chirumbolo, 2012). Several other molecules from medicinal plants are already clinically established for cancer treatment, for example alkaloids such as vinblastine and vincristine isolated from *Catharanthus roseus* (Gullett et al., 2010), combretastatins isolated from *Combretum caffrum* (Cirla and Mann, 2003), paclitaxel, obtained from *Taxus brevifolia* (Ludueno, 1998), camptothecin isolated from *Camptotheca acuminata* and homoharringtonine isolated from *Cephalotaxus harringtonia* (Aboul-Enein et al., 2014). Phytochemicals and nutraceuticals have frequently many molecular targets. Targets of natural products include: Aurora-A, Cdc2, Cdc25a, Cyclin B1, Cyclin D1, E2F4, RB, FoxM1, Skp2, p16, p21, p27 (cell cycle), EGFR, IGF-I, IGF-II, IGF-1R, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-5, ERK, JNK/c-Jun, p38, Akt, mTOR, PI3K, PTEN, 4E-BP1, G3BP1, Ras, ErbB2 (growth factor signaling), androgen receptor, estrogen receptors (ER α , ER β), (hormone signaling), FOXO, C/EBP α , BTG3, PHB, Pin1, PKC α , PKC δ , RAR α , RAR β , VDR, telomerase (Non-classified targets). Targets involving apoptotic pathways include Apaf-1, GDF15, BAD, Bax, Bcl-2, Bcl-xL, Bcl-xS, caspases 3, 8, 9, and 10, cIAP1, XIAP, DR5, Fas, Hsp70 and survivin. Phytochemicals are also involved in other cell activities such as cell metabolism modification (SphK1, HIF-1 α , FASN, HMG-CoA reductase, AMPK, PFKFB4), drug resistance inhibition (MRP5, BCRP, P-glycoprotein), genome stability (ATM/Chk1, BRCA1, BRCA2, p53, topoisomerase-II), inhibition of immune evasion (IL-10, IDO, TGF β), inhibition of invasion, metastasis and angiogenesis (E-cadherin, CXCL1, CXCL2, CXCL12, CXCR4, EMMPRIN, connexin 43, KAI1, c-Met, endoglin, VEGF/VEGFR, vimentin, ZEB1, MMP-2, -7, -9, PAK1) and stemness inhibition (Gli1, WIF-1, Wnt/ β -catenin, Notch-1, Notch-2, Twist-1), antioxidant/carcinogen metabolism (hSULT1A1, hSULT2A1, UGT1A, QR, GST, Nrf2, ARE, CYP1A1, metallothionein), anti-inflammation (IL-1RI, CCL2, NF- κ B, IKK, COX-1, COX-2, PGE2, iNOS, PPAR γ) (Gonzalez-Vallinas et al., 2013). However, in this section, we will discuss the most currently investigated targets of plants and their derived molecules as well as those involved in cancer drug resistance.

ABC Transporters and Drug Resistance

The adenosine triphosphate (ATP)-binding cassette (ABC) proteins are amongst the largest protein families found in all living organisms from microbes to humans (Efferth and Volm, 2017). The roles of ABC transporters include binding to and hydrolysis of ATP to fuel energy-dependent efflux of specific compounds across the membrane or to return them from the inner to the outer surface of membranes (Dean, 2009). Malignant cells resist to anticancer drugs by mutation or overexpression of drug targets, as well as by inactivation or efflux of the compounds to prevent cytotoxic drug concentrations sufficient to kill tumor cells (Gottesman et al., 2006). Human ABC transporters involved in drug resistance include ABCA3 or ABC3/ABCC (ABCA family), ABCB1 or MDR1/P-glycoprotein (P-gp) (ABCB family), ABCC1 or MRP1 and ABCC3 or MRP3/cMOAT-2 (ABCC family), ABCG2 or ABCP/MXR/BCRP (ABCG family) (Glavinas et al., 2004). The roles of P-gp, multidrug-resistance-proteins (MRPs) and breast cancer resistance protein (BCRP) in cancer drug resistance have been intensively investigated (Efferth, 2001; Gillet et al., 2007).

P-glycoprotein (P-gp)

P-gp is encoded by the *ABCB1/MDR1* gene and was identified as the first ABC transporter to be overexpressed in multidrug resistant cancer cell lines (Kartner et al., 1985). P-gp transports and/or secretes substrates in normal tissues such as the kidney, liver, colon, and adrenal gland as well as in the blood-brain, blood-placenta, and blood-testis barriers to protect these tissues from harmful compounds (Katayama et al., 2014). P-gp is involved in the efflux of doxorubicin, daunorubicin, vincristine, etoposide, colchicine, camptothecins and methotrexate, leading to resistance of cancer cells to these molecules (Dean, 2009). Clinical trials with synthetic drugs undertaken since 1994 have not resulted in significant progress in the discovery of new blockbusters for chemotherapy (Dean et al., 2005). Combating cancer-drug-resistance with phytochemicals inhibiting *ABCB1* could therefore be a more promising strategy to overcome multidrug resistance (MDR). Additionally, other ABC transporters such as *ABCC1/MRP1* (Cole et al., 1992) and *ABCG2* (Kim et al., 2002) are also overexpressed in cancer cells and could be targeted by plant products.

Multidrug-Resistance-Related Proteins (MRPs)

MRPs comprise of at least 9 types of transporters termed MRP1-9. They transport a wide array of structurally diverse molecules across cell membranes. They are involved in the absorption, disposition, and elimination of compounds in the body (Tian et al., 2005). MRPs are ATP-dependent efflux pumps having broad substrate specificity for the transport of endogenous substances such as glutathione conjugates (leukotriene C4 for MRP1, MRP2, and MRP4), bilirubin glucuronosides (MRP2 and MRP3), and cyclic AMP and cyclic GMP (MRP4, MRP5, and MRP8) as well as xenobiotic anionic substances localized in cellular plasma membranes (Keppler, 2011). Their overexpression in malignant cells is associated with resistance to a number of important cytotoxic drugs. MRPs are involved in the efflux of several anticancer

drugs such as doxorubicin, daunorubicin, vincristine, etoposide, colchicine, camptothecins, methotrexate (MRP1), vinblastine, cisplatin, doxorubicin, methotrexate (MRP2), methotrexate, etoposide (MRP3), 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), methotrexate (MRP4), 6-MP and 6-TG (MRP5), etoposide (MRP6) and 5-fluorouracil (MRP8) (Dean, 2009).

Breast Cancer Resistance Protein (BCRP, ABCG2)

MXR alias BCRP is an ABC transporter that plays a role in absorption, distribution, metabolism and excretion in normal tissues (Natarajan et al., 2012). Its overexpression in tumor cells confers resistance to chemotherapy by active extrusion of cytotoxic compounds. BCRP is involved in the efflux of mitoxantrone, topotecan, doxorubicin, daunorubicin, irinotecan, imatinib, and methotrexate (Dean, 2009). This receptor protein is involved in MDR of several tumor types including: acute leukemia and other hematological malignancies, head and neck carcinoma, breast cancer, lung cancer, brain tumors, hepatocellular carcinoma, gastrointestinal cancers such as pancreatic, colon, gastric and esophageal carcinomas (Natarajan et al., 2012).

Epidermal Growth Factor Receptor (EGFR/ErbB-1/HER1)

The epidermal growth factor receptor (EGFR; ErbB-1; HER1), a signal transducer for cell growth and differentiation, is the cell-surface receptor belonging to the ErbB family of receptors. This family consists of four closely related receptor tyrosine kinases, namely EGFR/HER1/ErbB-1, HER2/c-neu/ErbB-2, HER3/ErbB-3, and HER4/ErbB-4. Mutations affecting the activity or expression of EGFR can contribute to carcinogenesis (Zhang et al., 2007). Upon stimulation by ligands, EGFR is activated through homodimerization or heterodimerization and transmit signals to downstream substrates such as PI3K/AKT, RAS/RAF/MAPK, and STAT3/5 pathways, leading to cell proliferation and cell survival (Ji, 2010). Downstream substrates of EGFR have been found responsible for drug resistance meanwhile activation of PI3K/AKT pathway is essential for cancer cell survival (Ji, 2010). ErbB family receptors represent important targets of anticancer therapeutics such as tyrosine kinase inhibitors (TKIs; for example gefitinib and erlotinib) (Zhang et al., 2007).

Human Tumor Suppressor Protein p53

The tumor suppressor protein *p53* is encoded by the *TP53* gene in human beings and *Trp53* gene in mice. It is crucial in multicellular organisms, where it prevents cancer formation, thus, functions as a tumor suppressor (Surget et al., 2013). The gene *p53* is involved in the regulation of cell fate in response to different stresses in normal cells through the differential regulation of gene expression. Abnormal *p53* expression actively contributes to cancer formation and progression in malignant cells. The gene *p53* is also associated with response to cancer treatment by regulating apoptosis, genomic stability, and angiogenesis. Overexpression of mutated *p53* with reduced or abolished function is often associated with resistance to various

cytotoxic drug such as cisplatin, temozolomide, doxorubicin, gemcitabine, tamoxifen, and cetuximab (Hientz et al., 2017).

Caspases as Anticancer Drug Target

Caspases or cysteine-aspartic proteases are a family of protease enzymes essential for programmed cell death and inflammation. There are 14 mammalian caspases, 12 of which are of human origin (caspases 1–10, 12, and 14). They can be classified into three main types, that are initiator caspase (2, 8, 9, and 10), executioner or effector caspases (3, 6, and 7) and inflammatory caspases (1, 4, 5, 11, and 12) (Galluzzi et al., 2016). Caspase-14 plays a role in epithelial cell keratinocyte differentiation, and forms an epidermal barrier that protects against dehydration and UVB radiation (Denecker et al., 2008). Upon activation, caspases cleave a variety of substrates including: proteins involved in signal transduction (apoptosis regulators, cytokines, serine/threonine kinases), structural proteins (cytoskeletal and nuclear) and proteins involved in regulation of transcription, translation and RNA editing (Howley and Fearnhead, 2008). Deregulation of caspase activation or expression also leads to neurodegenerative and autoinflammatory disorders (Howley and Fearnhead, 2008). Initiator caspase-9 is activated in the apoptosome, while caspase-2 is activated in the PIDDosome and caspase-8 or -10 in the death-inducing signaling complex (DISC) (Howley and Fearnhead, 2008). Activated initiator caspases activate effector caspases, which in turn cleave structural and regulatory proteins culminating in the features of apoptosis. The search for caspase modulators is a novel attractive therapeutic approach in cancer research (Howley and Fearnhead, 2008).

Mitochondria as Anticancer Drug Target

Mitochondria play a central role in cellular metabolism, calcium homeostasis, redox signaling, and cell fate as main ATP source. During ATP biosynthesis, reactive oxygen species (ROS) are generated. In many cancer cells, mitochondria appear to be dysfunctional (due to a variety of factors, such as oncogenic signals and mitochondrial DNA mutations), with a shift in energy metabolism from oxidative phosphorylation to active glycolysis and an increase in the generation of ROS (Wen et al., 2013). The energy metabolism is different between normal and cancer cells, providing a scientific basis for development of strategies to selectively target malignant cells. As a result of mitochondrial dysfunction, cancer cells rely more on the glycolytic pathway in the cytosol to generate ATP. Key enzymes in this pathway such as hexokinase II, glyceraldehyde 3-phosphate dehydrogenase (overexpressed in malignant cells) therefore became potential therapeutic targets (Wen et al., 2013). Mitochondria-targeting compounds can kill drug-resistant cancer cells due to their ability to initiate mitochondrial outer membrane permeabilization in mitochondria, independently of other upstream signaling processes that may be impaired in cancer cells (Fulda and Kroemer, 2011). Some potential therapeutic targets associated with mitochondria include NADPH oxidases (NOX), the translocator protein (TSPO), the mitochondrial protein known as complement component 1, q subcomponent-binding protein (C1qBP) and the monocarboxylate transporters (MCTs) (Wen et al., 2013). Compounds known to target

the mitochondrial membrane potential are for instance the natural alkaloid pancratistatin, rhodamine-123, 4-phenyl-2,7-di(piperazin-1-yl)-1,8-naphthyridine, 2,5-diaziridinyl-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone and edelfosine (Wen et al., 2013). Natural products such as curcumin, resveratrol, berberine and cerulenin target mitochondrial apoptotic pathway (Wen et al., 2013).

Reactive Oxygen Species and Cancer Chemotherapy

Reactive oxygen species are chemically reactive chemical species containing oxygen such as hydroxyl radical, peroxides, superoxide, and singlet oxygen. They are produced through multiple mechanisms depending on cell and tissue types by NOX complexes in cell membranes, mitochondria, peroxisomes and endoplasmic reticulum (Muller, 2000; Han et al., 2001). ROS not only induce apoptosis, but also regulate host defense genes or airway homeostasis (Conner et al., 2002; Rada and Leto, 2008). In malignant cells, ROS induce changes in cellular functions such as cell death, cell proliferation, migration and differentiation (Wen et al., 2013). Increased ROS levels and mitochondrial dysfunction make cancer cells more vulnerable than normal cells.

Angiogenesis as Anticancer Drug Target

Angiogenesis is a physiological process in embryogenesis, in wound healing and in the female reproductive cycle leading to the formation of new blood vessels from pre-existing ones (Kumaran et al., 2008; Birbrair et al., 2015). Angiogenesis is critical in cancer for growth and metastasis, as tumors cannot grow beyond 200–300 μm in diameter without recruitment of new blood vessels to maintain nutrients and oxygen supply (Kumaran et al., 2008). This also makes angiogenesis an ideal target for cancer treatment. Some established therapeutic strategies targeting angiogenesis include bevacizumab [antibody to vascular endothelial growth factor (VEGF)], sorafenib and sunitinib (tyrosine kinase inhibitors). Combretastatin (vascular disruptive agents) and endostatin (endogenous inhibitor) are currently in clinical trials (Kumaran et al., 2008).

MAP Kinase Signaling Pathways in Cancer Chemotherapy

The mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway or Ras-Raf-MEK-ERK pathway is one of the most important signal transduction pathways. The MAPK/ERK pathway regulates growth, proliferation, differentiation and survival of the cells. Its deregulation is observed in various diseases such as cancer, degenerative syndromes, immunological and inflammatory diseases, making it an important drug target (Orton et al., 2005). The activation of a MAPK employs a core three-kinase cascade consisting of a MAPK kinase kinase (MAP3K or MAPKKK), which phosphorylates/activates another MAPK kinase (MAP2K, MEK, or MKK), which in turn phosphorylates and activates more MAPKs. Upon activation, MAPKs can phosphorylate a variety of intracellular targets such as cytoskeletal elements, nuclear pore proteins, membrane transporters, transcription factors, and other protein kinases (Avruch et al., 2001). Mutations in

proteins of this pathway, for example in Ras and B-Raf lead to carcinogenesis. Compounds targeting MAPK pathways are therefore investigated as potential cancer drugs (Orton et al., 2005). In fact, the role of stress-activated pathways such as Jun N-terminal kinase and p38 in the prevention of malignant transformation has been shown (Dhillon et al., 2007).

CENTRAL, EASTERN AND WESTERN AFRICA PLANTS AND DERIVED MOLECULES AND THEIR ANTICANCER TARGETS

During the past decade, intensive investigations of African medicinal plants as potential anticancer drug candidates have been carried out by African scientists in collaboration with various research teams throughout the world. However, this work should be strengthened with particular emphasis on the study of mechanisms of action and the identification of the different molecular targets of bioactive substances. Here, we give an overview of the studies published so far on plants and products derived from CEWA as far as their molecular target are available. A synopsis of phytochemicals acting preferentially on cancer cell lines actively expressing drug targets such as ABC transporters, EGFR, p53 and BCRP (**Figures 1–3**) will also be given. For instance the degree of resistance (DR) determined as the ratio of IC_{50} value of the resistant/ IC_{50} sensitive cell line will be taken into account to consider samples with potential therapeutic values to combat MDR phenotypes. Hence, samples with hypersensitivity or collateral sensitivity (more active on resistant than on parental sensitive cells line with DRs below 0.90 as well as samples with regular sensitivity (DR between 0.91 and 1.19) will be discussed. According to the criteria of the American National Cancer Institute, 20 $\mu\text{g}/\text{mL}$ is the upper IC_{50} limit to be considered as promising for cytotoxic crude extracts (Suffness and Pezzuto, 1990). Meanwhile, a threshold of 4 $\mu\text{g}/\text{mL}$ or 10 μM (Boik, 2001; Brahemi et al., 2010) after 48–72 h incubation has been set to identify compounds with considerable cytotoxic activity.

Caspases Activators

Although many African plant extracts were poor caspase activators (Kuede and Efferth, 2015), several phytochemicals from the flora of CEWA were reported as caspase activators (**Tables 1, 2**). Some documented caspase 3/7 activators included: benzophenones: guttiferone E (**26**) (Kuede et al., 2013d) and isoxanthochymol (**30**) from *Garcinia punctata* Oliv. (Kuede et al., 2013d), flavonoids: 4-hydroxyflavone (**7**) and isobavachalcone (**27**) isolated from *Dorstenia barteri* Bureau (Kuede et al., 2011b, 2015c), 6,8-diprenylerydiol (**8**) isolated from *Dorstenia mannii* Hook.f. (Kuede et al., 2011b), cycloartocarpesin (**18**) from *Morus mesozygia* Stapf. (Kuede et al., 2015c), gancaonin Q (**24**) from *Dorstenia angusticornis* Engl. (Kuede et al., 2011b), isoflavonoids: 6 α -hydroxyphaseollidin (**9**) from *Erythrina sigmoidea* Hua (Kuede et al., 2014c), isoneorautenol (**29**) from *Erythrina excelsa* Baker (Kuede et al., 2014d), xanthenes: cudraxanthone I (**17**) from *Milicia excelsa*

TABLE 1 | Cytotoxic plants of Central, East and West Africa and their molecular targets.

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Aframomum arundinaceum</i> (Oliver & Hanbury) K. Schum (Zinziberaceae)/Western and Central Africa	Anti-helminthic; against body odor; toothache; fungal infections (Iane et al., 2005)	Aframodiol; 8(7),12-labdadien-15,16-diol; galanolactone; galanal A; galanal B; 1- <i>p</i> -menthene-3,6-diol; 1,4-dihydroxybenzene; naringenin; kaempferol-3,7,4'-trimethyl ether (Kueete et al., 2014a)	Cytotoxicity of fruit methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, HCT116 (<i>p53</i> ^{+/+}) cells, HCT116 (<i>p53</i> ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2014a)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.76); Normal sensitivity: MDA-MB-231-BCRP cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 1.02); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.95) (Kueete et al., 2014a)
<i>Aframomum polyanthum</i> K. Schum (Zinziberaceae)/Tropical Africa	Cancer (Kueete et al., 2014a, 2015b)	Aframodiol (Ayator et al., 1994)	Cytotoxicity of fruit methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231-BCRP cells, U87MG cells, U87MG.ΔEGFR cells (Kueete et al., 2014a, 2015b)	Hypersensitivity: MDA-MB-231-BCRP cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.89); U87MG.ΔEGFR cells vs. U87MG cells (D.R. < 0.51) (Kueete et al., 2014a)
<i>Abizia adianthifolia</i> (Schum.) (Fabaceae)/Angola (Angola), Benin, Cameroon, Central African Republic, Congo, DR Congo, Ivory Coast, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, Tanzania, Togo, Uganda	Treatment of skin diseases, bronchitis, eyes inflammation, tapeworm, headaches and sinusitis (Watt and Breyer-Brandwyk, 1962; Van Wyk and Gerickse, 2000)	Adianthifoliosides A, B, D (Haddad et al., 2003, 2004), lupeol and auranitamide acetate (Tamokou J. D. D. et al., 2012), prospapogenins (Haddad et al., 2002)	Cytotoxicity of the methanol extract from bark and roots toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231-BCRP cells, HCT116 (<i>p53</i> ^{+/+}) cells, HCT116 (<i>p53</i> ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2016e)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R.: 0.43 (bark extract) and 0.39 (roots extract)); Roots methanol extract induces apoptosis in CCRF-CEM cells through caspases activation and MMP loss (Kueete et al., 2016e)
<i>Alchornea cordifolia</i> (Schum. & Thonn.) Müll.-Arg. (Euphorbiaceae)/Tropical Africa from Senegal to Kenya and Tanzania and throughout Central Africa to Angola	Treat rheumatic pains, fever, wounds, diarrhea, convulsions, coughs, gonorrhoea, yaws, ulcer, rheumatic pains, bronchial troubles (Ogunbamila and Samuelsson, 1990; Adeneye et al., 2014)	Alchorneol, alchorneone, gentisic acid and yohimbine (Ogunbamila and Samuelsson, 1990)	Cytotoxicity of the methanol extract from bark and roots toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231-BCRP cells, HCT116 (<i>p53</i> ^{+/+}) cells, U87MG cells, U87MG.ΔEGFR cells (Kueete et al., 2016e)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R.: 0.83 (bark extract) and <0.40 (bark extract)); Leaves methanol extract induces apoptosis in CCRF-CEM cells through MMP loss and increase ROS production (Kueete et al., 2016e)
<i>Annona muricata</i> Lin. (Annonaceae)/Tropical Africa including Cameroon and Nigeria	Treatment of wounds and insomnia; antiparasitic, insecticidal (Rajeswari et al., 2012)	Epomuricinens-A and B, muricetin, muricidins-3 and 4, muricadienin and chatenaytrienins-1, 2 and 3 and sabadalin, murihexol, donhexocin, ammonacin A and ammonacin B (Rajeswari et al., 2012), Annonamuricin E (Zorofchian Moghadamjousi et al., 2015)	Cytotoxicity of fruit pericarp, leave and seeds methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells (Kueete et al., 2016b), HL60 cells, HL60AR cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231-BCRP cells, HCT116 (<i>p53</i> ^{+/+}) cells, HCT116 (<i>p53</i> ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2016c)	Induced apoptosis in CCRF-CEM cells mediated by MMP loss (Kueete et al., 2016b); Capsules consisted of 100% pure, finely milled leaf/stem powder of the plant with no binders or fillers induces necrosis of PC cells by inhibiting cellular metabolism, downregulated the expression of molecules related to hypoxia and glycolysis in PC cells (Torres et al., 2012); Ethyl acetate extract of leaves reduces the colonic aberrant crypt foci formation in rats and induced down-regulation of PCNA and Bcl-2 proteins and the up-regulation of Bax protein (Zorofchian Moghadamjousi et al., 2015)
<i>Anonidium mamif</i> (oliv) Engl. et Diels. (Annonaceae)/Central and West Africa, including the DR Congo, Congo, Central African Republic, Angola, Ghana, Nigeria, Gabon and Cameroon	Treatment of sore feet, spider bite, bronchitis, dysentery, sterility caused by poison, gastroenteritis (Thomas et al., 2003); syphilis, infectious diseases (Noumi and Eloumou, 2011); diarrhea, snake bite, malaria (Betti, 2004), cancer (Kueete et al., 2013a)	Alkaloids, phenols, saponins, tannins, steroids, triterpenes (Kueete et al., 2013a)	Cytotoxicity of the methanol extract from leaves toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231-BCRP cells, HCT116 (<i>p53</i> ^{+/+}) cells, HCT116 (<i>p53</i> ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2013a)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R.: < 0.41); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.: 0.95); induces apoptosis in CCRF-CEM cells by disruption of MMP and increase ROS production (Kueete et al., 2013a)

(Continued)

TABLE 1 | Continued

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Anthocleista schweinfurthii</i> Gilg. (Loganiaceae)/Tropical Africa—Nigeria to Ethiopia, south to Angola, Zambia and Tanzania	Treatment of hernia, female sterility, stomach-ache in women, ovarian problems, venereal diseases, bronchitis, fever, purgative, malaria, hard abscesses arithemintic, otitis, pain, malaria, cancers, venereal diseases, bacterial diseases (Ngbolua et al., 2014)	Polyphenols, alkaloids, terpenes and steroids (Ngbolua et al., 2014), schweinfurthin 1, baurenone 2, baurenonol 3, 1-hydroxy-3,7,8 trimethoxy-xanone 4 and 1, 8-dihydroxy-3, 7 dimethoxy-xanone 5 (Mbougouere et al., 2007)	Cytotoxicity of fruit methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCAP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells (Kueete et al., 2016a)	Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 1.11); HCT116 (p53 ^{-/-}) vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.96) (Kueete et al., 2014a)
<i>Beilschmiedia acuta</i> Kosterm (Lauraceae)/Cameroon, Central African Republic	Treatment of cancer and gastrointestinal infections (Kueete et al., 2014e)	Flavonoids, triterpenes, phenols, saponins, alkaloids (Kueete et al., 2014e)	Cytotoxicity of the methanol extract from roots toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG- Δ EGFR cells (Kueete et al., 2014e)	Hypersensitivity (leaves extract): HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 0.29); induces apoptosis in CCRF-CEM cells (Kueete et al., 2014e)
<i>Calliandra portoricensis</i> (Jacq.) Benth. (Fabaceae)/Ghana, Nigeria, Uganda	Treatment of lumbago, pain relief, prostate diseases, and constipation, gonorrhoea, headaches and ophthalmic preparation (Adaramoye et al., 2015)	Saponins, tannins, flavonoids and glycosides (Aguwa and Lawal, 1988)	Cytotoxicity of the root methanol extract toward PC-3 cells and LNCaP cells (Adaramoye et al., 2015)	Antiangiogenic activity via inhibition of the growth of blood capillaries on the chicken chorioallantoic membrane, induces DNA fragmentation in PC-3 cells and LNCaP cells (Adaramoye et al., 2015)
<i>Dorstenia psilurus</i> Welwitsch (Moraceae)/Tropical Africa including Angola, Cameroon, Uganda, Tanzania, Malawi, Mozambique	Treatment of arthralgia, cardiovascular disorders, rheumatism, snakebites, headache, stomach disorders, diuretic, tonic, stimulant, analgesic, cancer (Ruppelt et al., 1991; Adjanihou et al., 1996; Ngadjui et al., 1998; Dimo et al., 2001; Kueete et al., 2011a)	Psoralen; 2-sitosterol glucoside analgesic (Ngadjui et al., 1998), dorsilurins C, F-K (Tabopoda et al., 2008)	Cytotoxicity of twigs methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells (Kueete et al., 2011a), HL-60 cells and PC-3 cells (Pleme et al., 2013)	Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.88) (Kueete et al., 2011a), induces apoptosis on HL-60 cells by the generation of ROS, MMP loss, modification in the DNA distribution and enhance of G2/M phase cell cycle (Pleme et al., 2013)
<i>Echinops giganteus</i> var. <i>leiji</i> (C. D. Adams) A. Rich. (Compositae)/Cameroon, Ethiopia, Rwanda, Sudan, Tanzania, Uganda, DR Congo	Treatment of cancer, heart and gastric troubles (Tene et al., 2004; Kueete et al., 2011a)	Lupol, sitosterol, β - <i>D</i> -glucopyranoside oleanolide, tetrahydrofuran-ceramide, β -amyrin acetate (3), 2-(penta-1,3-dienyl)-5-(4-hydroxybut-1-ynyl)-thiophene, 2-(penta-1,3-dienyl)-5-(3,4-dihydroxybut-1-ynyl)-thiophene, 4-hydroxy-2,6-di-(3',4'-dioxabicyclo-(3,3,0)octane (Tene et al., 2004; Sandjo et al., 2016), 2-(penta-1,3-dienyl)-5-(4-hydroxybut-1-ynyl)-thiophene, candidone, ursolic acid and 4-hydroxy-2,6-di-(3',4'-dimehoxyphenyl)-3,7-dioxabicyclo-(3,3,0)octane (Kueete et al., 2013c)	Cytotoxicity of rhizomes methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells (Kueete et al., 2011a), HL60AR cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCAP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2013c)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 0.82); Normal sensitivity: U87MG- Δ EGFR cells vs. U87MG cells (D.R. 0.92); (Kueete et al., 2013c); induces apoptosis in CCRF-CEM cells via the loss of MMP (Kueete et al., 2013c)

(Continued)

TABLE 1 | Continued

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Eleocharbia drupifera</i> (Thonn.) Stapf. (Euphorbiaceae)/from Guinea east to Uganda and from DR Congo and Angola	Treatment of hypertension and diabetes (Eno and Azah, 2004)	Euphol, tirucalol, euphorbol, ingenol eleoaphorbate, epitaraxerol, taraxerone, friedelin, lup-20(29)-en-3-one or lupenone, lupol, olean-12-ene-3-one, olean-12-ene-3-ol, eleoaphorbate (Kinghorn and Evans, 1974; Ahiashonu and Goodenowe, 2007), stigmasterol and β -sitosterol, sitosterol- <i>O</i> - β -D-xylopyranoside, 3,3',4'-tri- <i>O</i> -methylglagic acid, afzeilin and quercetin-3- <i>O</i> - β -D-xylopyranoside, 3,3',4'-tri- <i>O</i> -methylglagic acid 4- <i>O</i> - β -D-glucopyranoside, ellagic acid-4- <i>O</i> - β -xylopyranoside-3,3',4'-trimethyl ether (Voukeng et al., 2017)	Cytotoxicity of the methanol extract from leaves toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, HCT116 ($p53^{+/+}$) cells, HCT116 ($p53^{-/-}$) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2013e)	Hypersensitivity: U87MG- Δ EGFR cells vs. U87MG cells (D.R.: 0.68); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.: 1.12); HCT116 ($p53^{-/-}$) cells vs. HCT116 ($p53^{+/+}$) cells (D.R.: 1.13) (Kueete et al., 2013e)
<i>Enterolobium cyclocarpum</i> (Jacq.) Griseb. (Fabaceae)/West Africa	Treatment of inflammations, tumors, cold and bronchitis (Burkill, 1985)	D-Limonene, terpineol, eugenol and <i>d</i> -(+)-pinitol (Sowemimo et al., 2015)	Cytotoxicity of the methanol extract from leaves toward HeLa cells and MCF7 cells (Sowemimo et al., 2015)	Induces apoptosis and cells cycle arrest G2/M phase in HeLa cells and G1/G0 in MCF7 cells; causes phosphatidylserine translocation (Sowemimo et al., 2015)
<i>Erythrina sigmoidea</i> Hua (Fabaceae)/Cameroon, Chad	Used as antidotes (venomous stings, bites, etc.), diuretic, febrifuge and Treatment of arthritis, rheumatism, pulmonary troubles, stomach troubles, infectious diseases and kidney diseases (Burkill, 1985), gastrointestinal infections, venereal diseases and leprosy (Mabeku et al., 2011)	6 α -hydroxyphasecolidin (9), atalantoflavone (15), bidwillon A (16), neobavaisoflavone (35), neocyclomorusin (36), and Sigmoidin I (44) (Kueete et al., 2014c) (Kueete et al., 2014c)	Cytotoxicity of bark methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, HCT116 ($p53^{+/+}$) cells, HCT116 ($p53^{-/-}$) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2016a)	Hypersensitivity: HCT116 ($p53^{-/-}$) cells vs. HCT116 ($p53^{+/+}$) cells (D.R. 0.83); U87MG- Δ EGFR cells vs. U87MG cells (D.R. 0.68); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 1.08); induces apoptosis in CCRF-CEM leukemia cells via disruption of the MMP (Kueete et al., 2014a)
<i>Gladiolus quarinianus</i> A. Rich (Iridaceae)/Cameroon, Senegal to Ethiopia	Treatment of gastrointestinal infections and cancer (Kueete et al., 2013a)	Alkaloids, anthocyanins, anthraquinones, phenols, saponins, tannins, sterols, triterpenes (Kueete et al., 2013a)	Cytotoxicity of the methanol extract from whole plant toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($p53^{+/+}$) cells, HCT116 ($p53^{-/-}$) cells, U87MG- Δ EGFR cells (Kueete et al., 2013a)	Hypersensitivity: U87MG- Δ EGFR cells vs. U87MG cells (D.R.: <0.85); Normal sensitivity: HCT116 ($p53^{-/-}$) cells vs. HCT116 ($p53^{+/+}$) cells (D.R.: 1.12); induces apoptosis in CCRF-CEM cells by disruption of MMP (Kueete et al., 2013a)
<i>Imperata cylindrica</i> Beauv. var. <i>koenigii</i> Durand et Schinz (Poaceae)/Benin, Burkina Faso, DR Congo, Ivory Coast, Gambia, Ghana, Guinea, Kenya, Liberia, Mali, Mozambique, Niger, Nigeria, Senegal, Tanzania, Togo, Uganda	Used as diuretic and anti-inflammatory and cancer agent (Nishimoto et al., 1968; Kueete et al., 2011a)	Jaceidin, quercetagetin-3, 5, 6, 3'-tetramethyl ether, β -Sitosterol-3- <i>O</i> - β -D-glucopyranosyl-6''-tetradecanoate (Mohamed et al., 2009), imperanene (Matsunaga et al., 1995)	Cytotoxicity of roots methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells, MiaPaca-2 (Kueete et al., 2011a), HL60 cells, HL60AR cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($p53^{+/+}$) cells, HCT116 ($p53^{-/-}$) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2013c); cytotoxicity of leaves methanol extract against SCC-9 cells (Keshava et al., 2016) and against HT-29 cells (Kwok et al., 2016)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM (D.R. 0.90) cells (Kueete et al., 2011a), apoptosis in CCRF-CEM cells via the loss of MMP (Kueete et al., 2013c); leaves methanol extract reduced the clonogenic potential and inhibited cell proliferation by arresting the cell cycle in the G2/M phase in SCC-9 cells as well as DNA fragmentation (Keshava et al., 2016); Induced G2/M arrest and apoptosis in HT-29 cells mediated by caspase 3/7 activation and ROS production (Kwok et al., 2016)

(Continued)

TABLE 1 | Continued

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Markhamia tomentosa</i> (Benth.) K.Schumex.Engl. (Bignoniaceae)/West Africa	Treatment of oedema, cancer, gout and scrotal elephantiasis, pulmonary troubles and general body pain (Burkhill, 1985; Ibrahim et al., 2013)	Pomolic acid, oleoanolic acid, tormentic acid, and β -sitosterol, pautownin, palmitone, palustrine, 2-acetylnaphthol[2,3-b] furan-4,9-dione, 2-acetyl-6-methoxy-naphthol[2,3-b] furan-4,9-dione, luteolin, luteolin-7-rutinoside, and luteolin-3',7'-di-O-glucoside (Ibrahim et al., 2016)	Cytotoxicity of the methanol extract from leaves toward HeLa cells (Ibrahim et al., 2013)	Induces apoptosis and cell cycle arrest in HeLa cells in the G0/G1; induces phosphatidylinositol translocation and depolarization MMP (Ibrahim et al., 2013)
<i>Morus mesozygia</i> Stapf. (Moraceae)/Tropical Africa, from Senegal eastward to Ethiopia and southward to Zambia, Angola, Mozambique	Treatment of arthritis, rheumatism, malnutrition, debility, pain-killers, stomach disorders, wound infections, gastroenteritis, peptic ulcer, infectious diseases (Burkhill, 1985; Kueete and Efferth, 2010, 2011)	moracins Q-U, 3beta-acetoxylurs-12-en-11-one, marsformoxide, moracin C, moracin M, moracin K, artocarpesin, cycloartocarpesin, morachalcone A (Kapche et al., 2009; Kueete et al., 2009); kushenol E, artochamin C, moracin C and moracin L (Nicolle et al., 2009)	Cytotoxicity of bark, methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, U87MG cells, HepG2 cells (Kueete et al., 2016a)	Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 1.04); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.95); U87MG. Δ EGFR cells vs. U87MG cells (D.R. 1.06) (Kueete et al., 2014a)
<i>Nauclea latifolia</i> Smith. (Rubiaceae)/West tropical Africa—from Ghana to Gabon and DR Congo	Treatment of gonorrhoea (Abbiw, 1990), hypertension (Akabue and Mital, 1982), gastrointestinal tract disorders (Machubanyi, 1995), prolong menstrual flow (Elujoba, 1995), stomach pain, constipation, fever, diarrhea, dysentery (Anowi et al., 2012)	Naucleamides A,B,C,D,E (Shigemori et al., 2003)	Cytotoxicity of bark and leave methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{-/-}) cells (Kueete et al., 2016a)	Hypersensitivity: MDA-MB-231-BCRP cells vs. MDA-MB-231-pcDNA cells (D.R. 0.80); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.88); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.98) (Kueete et al., 2014a)
<i>Nauclea pobeguinii</i> (Pobég. ex Pellegr.) Merr. ex E.M.A. (Rubiaceae)/South Tropical Africa: Angola, Zambia, West Tropical Africa: Burkina, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Nigeria, Senegal, Sierra Leone, West-Central Tropical Africa: Cameroon Central African Republic, Congo, DR Congo, Gabon	Used as abortive, Treatment of stomach ache, infectious diseases (Karou et al., 2011), jaundice (Kadiji et al., 2007), fever, diarrhea, worm, malaria (Mesia et al., 2005)	Nauclefine 1 and 2, strictosamide, carboxystrictosidine, methylangustoline, 3-O- β -D-fucosyl-quinovic-acid, 3-keto-quinovic-acid (Karou et al., 2011); angustoline (Zeches et al., 1985), 3-acetoxy-11-oxo-urs-12-ene, p-coumaric acid, citric acid trimethyl ester, resveratrol, resveratrol β -D-glucopyranoside, strictosamide (Kueete et al., 2015)	Cytotoxicity of the methanol extract from bark and leaves toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG. Δ EGFR cells (Kueete et al., 2015)	Hypersensitivity (bark extract): CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.: 0.80); MDA-MB-231-BCRP cells vs. MDA-MB-231-pcDNA cells (D.R.: 0.53); HCT116 (p53 ^{+/+}) cells vs. HCT116 (p53 ^{-/-}) cells (D.R.: 0.54); U87MG. Δ EGFR cells vs. U87MG cells (D.R.: 0.47)
<i>Pachypodanthium staudtii</i> Engl & Diels (Amonaceae)/Sierra Leone east to the Central African Republic and south to Gabon and DR Congo	Treatment of cancer, chest pain (Irvine, 1961); bronchitis (Bouquet and Debray, 1974) and oedema (Ngaadjui et al., 1989)	Pachypodol, 2,4,5-Trimethoxystyrene, Pachypophyllin, pachyposaudins A and B (Ngaadjui et al., 1989), Sabinene, β -elemene, E- β -carophyllene, β -selinene, β -bisabolene, δ -cadimene, 2,4,5-trimethoxy-1-vinylbenzene (Vapi et al., 2012)	Cytotoxicity of leave, bark and roots methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, HepG2 cells (Kueete et al., 2016b)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.87); MDA-MB-231-BCRP cells vs. MDA-MB-231-pcDNA cells (D.R. 0.90); Normal sensitivity: U87MG. Δ EGFR cells vs. U87MG cells (D.R. 1.05) (Kueete et al., 2016b)

(Continued)

TABLE 1 | Continued

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Passiflora edulis</i> Sims (Passifloraceae)/Central and East including Cameroon, Tanzania, Uganda	Treatment of cancer, fungal infections, inflammation, insomnia and anxiety, antihypertensive (Chimura et al., 2006), gastric trouble (Silva et al., 2006), antioxidant (Kamman et al., 2011)	Ionone-I, ionone-II, megastigma-5,8-dien-4-1, megastigma-5,8(Z)-diene-4-1, 4,4a-Epoxy-4, 4a-dihydroedulan, 3-hydroxyedulan, edulan-I, edulan-II, passifloric acid methyl ester (Kannan et al., 2011)	Cytotoxicity of fruit pericarp and fruit methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells (Kueite et al., 2016b)	Induces apoptosis in CCRF-CEM cells mediated by MMP loss (Kueite et al., 2016b); fruit juice reduces the number, size, and invasiveness of transformation foci in a BALB/c 3T3 neoplastic transformation model; activated caspase-3 in MOLT-4 cells (Rowe et al., 2004)
<i>Piper capense</i> L.f. (Piperaceae)/from Guinea to Ethiopia and south to Angola, Mozambique	Sleep inducing remedy, anthelmintic, anticancer (Kokowaro, 1976; Van Wyk and Gerlicke, 2000; Kueite et al., 2011a)	Kaouine, Z-antiepilepsimine (Kaou et al., 2010), piperine, 4,5-dihydropiperine (Pedersen et al., 2009), beta-pinene, sabinene, alpha-pinene (Woguem et al., 2013)	Cytotoxicity of seeds methanol extract toward CCRF-CEM cells and CEM/ADR5000 (Kueite et al., 2011a), MDA-MB-231 cells, A375 cells, HCT116 cells (Woguem et al., 2013), HL60 cells, HL60AR cells, MDA-MB-231-pcDNA cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG-ΔEGFR cells, HepG2 cells (Kueite et al., 2013c)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.90) (Kueite et al., 2011a), apoptosis in CCRF-CEM cells via the loss of MMP and increase ROS production (Kueite et al., 2013c)
<i>Polyscias fulva</i> (Hiem) Harms. (Araliaceae)/Tropical Africa - Sierra Leone to Sudan, Ethiopia to Angola, Zambia and Mozambique	Malaria, fever, mental illness (Tshibangu et al., 2002); venereal infections and obesity (Jenuto et al., 2007; Fochu et al., 2009) and cancer (Kueite et al., 2014e)	Polysciasoside A, kalopanax-saponin B, alpha-hederin (Bedir et al., 2001; Kueite and Efferth, 2011)	Cytotoxicity of the methanol extract from roots and leaves toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG-ΔEGFR cells, HepG2 cells (Kueite et al., 2014e)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 0.41); induces apoptosis in CCRF-CEM cells via the alteration of MMP and enhanced ROS production (Kueite et al., 2014e)
<i>Sclerocarya birrea</i> (A. Rich.) Hochst. (Anacardiaceae)/throughout most of sub-Saharan Africa outside the humid forest zone, from Mauritania and Senegal to Ethiopia and Eritrea, Botswana, Mozambique	Treatment of stomach aches, diarrhea, wounds, coughs (Gouwakinnou et al., 2011)	Quercetin 3-O-alpha-L-(6"-galloyl)-arabinocturanoside, quercetin 3-O-beta-D-(6"-galloyl)glucopyranoside, quercetin 3-O-alpha-L-rhamnopyranoside, kaempferol galloyl/galactopyranoside, quercetin 3-O-beta-D-(6"-galloyl)glucopyranoside, quercetin 3-O-beta-D-glucopyranoside, myricetin 3-O-alpha-L-rhamnopyranoside, and kaempferol 3-O-alpha-L-rhamnopyranoside, gallic acid, (-)-epicatechin 3-O-galloyl ester, (-)-epigallocatechin 3-O-galloyl ester (Briaca et al., 2003), terpinen-4-ol, pyrrolidine, aromadendrene, alpha-gurjunene (Njume et al., 2011)	Cytotoxicity of the methanol extract from roots toward HepG2 cells (Armentano et al., 2015)	Induces apoptosis via ROS production in HepG2 cells (Armentano et al., 2015)
<i>Tridestromon omphalocarporoides</i> Engl. (Sapotaceae)/Cameroon, Gabon, Congo, DR Congo	Treatment of gastroenteritis and skin lesions (Kueite et al., 2006)	Alkaloids, phenols, polyphenols, saponins, tannins, triterpenes, anthraquinones and steroids (Kueite et al., 2006)	Cytotoxicity of bark, methanol extract toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells (Kueite et al., 2016a)	Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.99); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 1.15) (Kueite et al., 2014a)

(Continued)

TABLE 1 | Continued

Plant species and family/distribution in Central, East and West Africa	Traditional uses	Bioactive or potentially bioactive components	Reported cytotoxic activity*	Molecular targets and/or effects on resistant cells
<i>Lapaca togoensis</i> Pax (Euphorbiaceae)/Tropical Africa from Sierra Leone to DR Congo; Predominant in Cameroon	Antiemetic, lotion for skin disorders (Mwngome et al., 2010), remedy for pneumonia, cough, fever, rheumatism, vomiting, epilepsy (Kone et al., 2008) and bacterial diseases (Kone et al., 2004)	β -amyrin acetate, 11-oxo- α -amyrin acetate, lupeol, pomolic acid, furokadsurin B, arborinin, 3-O- β -D-glucopyranosyl sitosterol (Kueete et al., 2015e)	Cytotoxicity of the methanol extract from fruit toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 0.84); Normal sensitivity; CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.: 1.05); U87MG- Δ EGFR cells vs. U87MG cells (D.R.: 1.08); induces apoptosis in CCRF-CEM cells by MMP loss (Kueete et al., 2015e)	Hypersensitivity: MDA-MB-231-BCRP cells vs. MDA-MB-231-pcDNA cells (D.R.: 0.16); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 0.84); Normal sensitivity; CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.: 1.05); U87MG- Δ EGFR cells vs. U87MG cells (D.R.: 1.08); induces apoptosis in CCRF-CEM cells by MMP loss (Kueete et al., 2015e)
<i>Vepes soyaxii</i> Engl. (Rutaceae)/Throughout West Africa, from Sierra Leone, Liberia, Ivory Coast, Mali, Ghana to Nigeria and Cameroon	Anti-fibrinolytic, Treatment of stomachache, malaria (Momeni et al., 2010) and cancer (Kueete et al., 2013a)	Alkaloids, anthocyanins, phenols, tannins, steroids, triterpenes (Kueete et al., 2013a)	Cytotoxicity of the methanol extract from leaves toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231-pcDNA cells, HCT116 (p53 ^{-/-}) cells, HCT116 (p53 ^{+/+}) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2013a)	Hypersensitivity: U87MG- Δ EGFR cells vs. U87MG cells (D.R.: 0.47); Normal sensitivity; HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 1.12); induces apoptosis in CCRF-CEM cells mediated by disruption of MMP (Kueete et al., 2013a)
<i>Xylopi aethiopica</i> (Dunal) A. Rich. (Annonaceae)/Angola, Benin, Burkina Faso, Cameroon, Central African Republic, DR Congo, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Liberia, Mozambique, Nigeria, São Tomé and Príncipe, Senegal, Sierra Leone, Sudan, South Sudan, Tanzania, Togo, Uganda	Treatment of cancer, constipation; uterine hemorrhage, diuretic, fever (Iwu, 1993; Kueete et al., 2011a; Okator, 2012)	Volatile oil (Tatsadjieu et al., 2003), xylopic acid (Osato and Olibri, 2016), 6 α -hydroxy-ent-kauran-19- <i>oic</i> acid, 3',4',5-trihydroxy-6''- δ '', isoterandrine (51) and trans-tilioside (Kueete et al., 2015g)	Cytotoxicity of seeds methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells (Kueete et al., 2011a), C-33A cells, KB cells, MCF-7 cells (Adaramoye et al., 2011), HL60 cells, HL60AR cells, MDA-MB-231-pcDNA cells, MDA-MB-231-BCRP cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG- Δ EGFR cells, HepG2 cells (Kueete et al., 2013c)	Hypersensitivity: U87MG- Δ EGFR vs. U87MG (D.R. 0.53); Normal sensitivity; HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R.: 1.05)(Kueete et al., 2013c)(Kueete et al., 2013c)(Kueete et al., 2013c) C-33A cells, nuclear fragmentation, cells accumulation in sub-G0/G1, cycle arrest in G2, up-regulation of p53 and p21 genes, and an increase in the Bax/Bcl-2 ratio (Adaramoye et al., 2011), apoptosis in CCRF-CEM cells via the loss of MMP (Kueete et al., 2013c)
<i>Zanthoxylum usambarense</i> (Engl.) Kokwaro (Rutaceae)/East tropical Africa - Ethiopia, Kenya, Tanzania, eastern DR Congo	Treatment of malaria, upper respiratory tract infections, cough, rheumatism, tooth decay (Ozkan et al., 2013)	Carthin-6-one, pellitorine, oxychelelythine, norchelelythine, (+)-sesamin, (+)-piperitol-3,3-dimethylallyl ether (He et al., 2002)	Cytotoxicity of the aqueous-methanol 70% extract from aeral part toward MDA-MB-231 cells and MCF-7 cells (Ozkan et al., 2013)	Induces apoptosis in MCF7 cells (Ozkan et al., 2013)
<i>Zinziber officinale</i> Roscoe (Zingiberaceae)/Tropical Africa	Treatment of infectious diseases, respiratory tract infections, cancer, indigestion, diarrhea, nausea (Akoachere et al., 2002; Kato et al., 2006; Sakpakdejaroen and Itharat, 2009; Kueete et al., 2011a)	2-(4-hydroxy-3-methoxyphenyl)ethanol and 2-(4-hydroxy-3-methoxyphenyl)ethanoic acid (Kato et al., 2006), 6-shogaol (Kim et al., 2008), zingiberene, camphene, β -sesquiphellandrene, β -bisabolene, α -farnesene, curcumene, cineole, citral, terpineol, terpenes, borneol, β -elemene, zingiberenol, limonene, geraniol, zingiberol, linalool (Chrubasik et al., 2005; Ali et al., 2008; Mbaveng and Kueete, 2017)	Cytotoxicity of rhizomes methanol extract toward CCRF-CEM cells and CEM/ADR5000 cells, MiaPaca-2 cells (Kueete et al., 2011a), CL-6 cells (Plengsuriyakarn et al., 2012); cytotoxicity of essential oil against HeLa cells (Santos et al., 2016)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.88) (Kueete et al., 2011a); ethanol extract induces DNA fragmentation and up-regulation of MDR1 and MRP3 genes in CL-6 cells (Plengsuriyakarn et al., 2012)

*Reported cell lines: leukemia cells [CCRF-CEM, CEM/ADR5000, HL60, and HL60AR]; Carcinoma cells [A375 melanoma cells; C-33A and Caski cervix carcinoma cells; MDA-MB-231-pcDNA3 and MDA-MB-231-BCRP clone 23 breast cancer cells; HT-29, HCT116 (p53^{+/+}) and HCT116 (p53^{-/-}) colon cancer cells; KB and SCC-9 human oral squamous carcinoma cells; HeLa cervical carcinoma; HepG2 hepatocarcinoma; PC-3, MiaPaca-2 pancreatic cancer cells; LNCaP human prostatic adenocarcinoma, AML12 normal hepatocytes; BALB/c 3T3 fibroblasts]; D.R.: degree of resistance; D.R. is determined as the ratio of IC₅₀ value in the resistant cell line. AML12, HL60AR, CEM/ADR5000, MDA-MB-231-BCRP, HCT116 (p53^{-/-}) and U87MG- Δ EGFR were used as the corresponding resistant counterpart for HepG2, HL60, CCRF-CEM, MDA-MB-231-pcDNA, HCT116 (p53^{+/+}), U87MG, respectively; Hypersensitivity, D.R. < 0.90; Normal sensitivity, D.R. 1 to 1.19; MMP, mitochondrial membrane potential; ROS, reactive oxygen species; (-), not reported.

TABLE 2 | Bioactive compounds identified in cytotoxic plants of Central, East and West Africa and their molecular targets.

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
TERPENOIDS			
Alpha-hederin (triterpene glycoside; 1)	<i>Polyscias fulva</i> (Hiern) Harms. (Araliaceae) (Kueite et al., 2014e); <i>Clematis gampshiana</i> L. (Ranunculaceae), <i>Hedera</i> spp. (Nigella spp. (Cheng et al., 2014)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53+/+) cells, HCT116 (p53-/-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014e)	Genes closely associated with the response to alpha-hederin belong to diverse functional groups such as apoptosis, growth and cell cycle regulation, signal transduction, transcription, transport processes, nerve cell functions (Kueite et al., 2014e); induces disruption of MMP, caspase-3 activation, and increases the production of ROS in P388 cells, caspase-3 activation (Swamy and Huat, 2003); induces apoptosis in breast cancer cells, induces depolarization of MMP, promotes caspase-3 and caspase-9 activation. (Cheng et al., 2014); induces apoptosis, membrane permeabilization and morphologic changes in cancer cell lines through a cholesterol-dependent mechanism (Lorent et al., 2016); other molecular targets as identified by molecular docking simulations include Ras related protein rap-2a, cathepsin K, estradiol 17-beta dehydrogenase-1, GTPase HRas, cellular retinoic acid-binding protein 2, dihydroorotate dehydrogenase (Sridhar et al., 2014)
Galanol A (diterpene; 2)	<i>Aframomum arundinaceum</i> (Oliver & Harbury) K. Schum (Zingiberaceae)(Kueite et al., 2014a)	Cytotoxicity toward CCRF-CEM cells, MDA-MB-231- <i>BCRP</i> cells (Kueite et al., 2014a)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. <0.70) (Kueite et al., 2014a); induces apoptosis in Jurkat human T-cell leukemia cells through DNA fragmentation, MMP alteration and caspase-3 activation as well as downregulation of the anti-apoptotic Bcl-2 protein (Miyoshi et al., 2003)
PHENOLICS			
2,2',5,6'-tetrahydroxybenzophenone (benzophenone; 3)	<i>Hypericum lanceolatum</i> Lam. (Hypericaceae)(Kueite et al., 2013d)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53+/+) cells, HCT116 (p53-/-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2013d)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.24) (Kueite et al., 2013d)
2-acetyluro-1,4-naphthoquinone (naphthoquinone; 4)	<i>Newbouldia laevis</i> Seems. (Bignoniaceae) (Eyang et al., 2006; Kueite et al., 2007a)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, PF-382 cells, HL-60 cells, MiaPaCa-2 cells, Capan-1 cells, MCF-7 cells, SW-680 cells, 786-0 cells, U87MG cells, A549 cells, Colo-38 cells, HeLa cells, Caski cells (Kueite et al., 2011d)	Anti-angiogenic effects through inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs; induces apoptosis and cell cycle arrest in S-phase in CCRF-CEM (Kueite et al., 2011c)
3,4',5-trihydroxy-6'',6''-dimethylpyranol[2,3-g]flavone (flavonoid; 5)	<i>Xylopiya aethiopica</i> (Dunal) A.Rich. (Annonaceae) (Kueite et al., 2015g)	Cytotoxicity toward CCRF-CEM cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53+/+) cells, HCT116 (p53-/-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015g)	Normal sensitivity: HCT116 (p53-/-) cells vs. HCT116 (p53+/+) cells (D.R. 0.96); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 1.03); induces apoptosis in CCRF-CEM cells, mediated by MMP disruption (Kueite et al., 2015g)
4'-hydroxy-2',6'-dimethoxychalcone (flavonoid; 6)	<i>Polygonum limbatum</i> Meisn. (Polygonaceae) (Kueite et al., 2014b)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53+/+) cells, HCT116 (p53-/-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014b)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.0.27); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.33); Normal sensitivity: 231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.92); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 1.17); induced cell cycle arrest between Go/G1 phase and apoptosis in CCRF-CEM cells via disruption of MMP and increase ROS production (Kueite et al., 2014b)
4-hydroxylonchocarpin (flavonoid; 7)	<i>Dorstenia berteri</i> (Mbaveng et al., 2006; Kueite et al., 2010)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, HL-60 cells, MiaPaCa-2 cells, MCF-7 cells, 786-0 cells, U87MG cells, Colo-38 cells, HeLa cells, Caski cells (Kueite et al., 2011b)	Induces apoptosis in CCRF-CEM cells via caspase 3/7 activation; anti-angiogenic effect via inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs (Kueite et al., 2011b)
6,8-diprenylerioidictyl (flavonoid; 8)	<i>Dorstenia mannii</i> Hook f. (Ngaджу et al., 2000; Mbaveng et al., 2012)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, PF-382 cells, HL-60 cells, MiaPaCa-2 cells, MCF-7 cells, 786-0 cells, U87MG cells, A549 cells, Colo-38 cells, HeLa cells, Caski cells (Kueite et al., 2011b)	Induces apoptosis in CCRF-CEM cells via caspase 3/7 activation; anti-angiogenic effect via inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs (Kueite et al., 2011b)
8-hydroxydudraxanthone G (xanthone; 10)	<i>Garcinia nobilis</i> Enql. (Guttiferae) (Foutsisa et al., 2012, 2013)	Cytotoxicity toward CCRF-CEM cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53+/+) cells, HCT116 (p53-/-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2013b)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.74); HCT116 (p53-/-) cells vs. HCT116 (p53+/+) cells (D.R. 0.90); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.55) (Kueite et al., 2013b)

(Continued)

TABLE 2 | Continued

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
Alpinumisoflavone (flavonoid; 12)	<i>Ficus chlamydocarpa</i> Mildbr. & Burret (Moraceae) (Kueete et al., 2008)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2016c)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R.0.62); HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.86); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.90); induces apoptosis in CORF-CEM cells, mediated by loss of MMP and increase ROS production (Kueete et al., 2016c); induces apoptotic cell death in H2108 and H1299 cells, mediated by caspase 3/7 activation (Namkoong et al., 2011); induces apoptosis in esophageal squamous cell carcinoma by modulating miR-370/PIM1 signaling (Lian et al., 2016); increases the expression of microRNA precursor, miR-101 by suppressing Protein Kinase B (Akt) signaling in renal cell carcinoma (Wang et al., 2017)
Amentoflavone (flavonoid; 13)	<i>Dorstenia berteri</i> Bureau (Moraceae) (Mbaveng et al., 2008; Kueete et al., 2010)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells (Kueete et al., 2016c); MCF-7 cells (Chen et al., 2015), B16F-10 cells (Guruvayoorappan and Kuttan, 2009) and SW480 cells (Wang et al., 2014)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R.0.77); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.49). Normal sensitivity: HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 1.06) (Kueete et al., 2016c); downregulates cytokines mediated cyclooxygenase-2 and inducible nitric oxide synthase expression in A549 cells (Banerjee et al., 2002); reduces tumor nodule formation from B16F-10 melanoma-induced experimental lung metastasis in C57BL/6 mice, with inhibition of the expression of metalloproteinase-1 and 2 in lung tissue (Guruvayoorappan and Kuttan, 2007a); induces increase interleukin-2 and interferon-gamma production in Ehrlich ascites carcinoma-bearing BALB/c mice (Guruvayoorappan and Kuttan, 2007b); activates PPAR γ /PTEN expressions and induces apoptosis via suppressing E7 expression, cell cycle arrest at sub-G1 phase, and mitochondria-emanated intrinsic pathways in SHa and CaSki cells (Lee et al., 2011); induces apoptosis in MCF-7 cells via DNA fragmentation, and de-regulation of intracellular ROS and calcium, alters MMP and activates caspase 3 (Pei et al., 2012); induces anti-angiogenic and anti-metastatic effects through suppression of NF- κ B activation in MCF-7 cells (Chen et al., 2015)
Atrocarpin (flavonoid; 14)	<i>Morus mesozygia</i> Stapf (Moraceae) (Kapche et al., 2009; Kueete et al., 2009)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2015c)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R.0.78)(Kueete et al., 2015c)
Atlantoflavone (flavonoid; 15)	<i>Erythrina sigmoidea</i> Hua (Leguminosae) (Kueete et al., 2014c)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> , HCT116 ($\rho 53^{+/+}$), HCT116 ($\rho 53^{-/-}$), U87MG, U87MG.ΔEGFR, HepG2 (Kueete et al., 2014c)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.75); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.94) (Kueete et al., 2014c)
Bidwillon A (isoflavonoid; 16)	<i>Erythrina sigmoidea</i> Hua (Leguminosae) (Kueete et al., 2014c)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, HepG2 cells (Kueete et al., 2014c)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.<0.17); HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.88); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.39); Normal sensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 1.18) (Kueete et al., 2014c)
Oudraxanthone I (xanthone; 17)	<i>Millettia excelsa</i> Welw C.C. Berg. (Moraceae) (Kueete et al., 2013b)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2013b)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.78); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.36); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.85); induces apoptosis in CORF-CEM cells via the activation caspases 8 and 9 and caspase 3/7 and loss of MMP (Kueete et al., 2013b)
Cycloartocarpin (flavonoid; 18)	<i>Morus mesozygia</i> Stapf (Moraceae) (Kapche et al., 2009; Kueete et al., 2009)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2015c)	Normal sensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R.1.04); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.1.05); induces apoptosis in CORF-CEM cells, mediated by caspase 3/7, caspase 8 and 9 activation and the disruption of MMP (Kueete et al., 2015c)
Damnacanthol (anthraquinone; 19)	<i>Pentstemon schimperii</i> (Hook.f.) Verde (Rubiaceae) (Kueete et al., 2015a); <i>Morinda citrifolia</i> (Shaghayegh et al., 2016)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueete et al., 2015b) (Kueete et al., 2015a)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.29); Normal sensitivity: HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 1.05); induces apoptosis and cell cycle arrest in G1 phase, stimulates <i>p53</i> and <i>p21</i> genes and activates caspase-7 in MCF-7 cells (Aziz et al., 2014); induces apoptosis in CORF-CEM leukemia cells via disruption of the MMP and increase in ROS production (Kueete et al., 2015b); induces apoptosis through inhibition of c-Met in HepG2 cells (García-Villas et al., 2015); induces apoptosis and cell cycle arrest in oral cancer H460 oral squamous carcinoma cells through DNA fragmentation and activation of intrinsic apoptosis pathway (Shaghayegh et al., 2016)

(Continued)

TABLE 2 | Continued

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
Dannacanthol (anthraquinone; 20)	<i>Pentstemon schimperii</i> (Hook f.) Verde (Rubiaceae) (Kueete et al., 2015a)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2015a)	Hypersensitivity: HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.77); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 1.09); U87MG. Δ EGFR cells vs. U87MG cells (D.R. 1.10); induces apoptosis in CORF-CEM leukemia cells via disruption of the MMP and increase in ROS production (Kueete et al., 2015a)
Dorsmanin F (flavonoid; 21)	<i>Dorstenia mannii</i> Hook.f. (Moraceae) (Ngadjui et al., 1999a)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2015d)	Hypersensitivity: U87MG. Δ EGFR cells vs. U87MG cells (D.R. 0.61); induces apoptosis in CORF-CEM cells via the disruption of MMP (Kueete et al., 2015d)
Euxanthone (xanthone; 22)	<i>Orcia suaveolens</i> Engl. (Rutaceae) (Fouotisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2016c); HeLa cells, CEM-SS cells and CaOV3 cells (Ee et al., 2005)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0. <0.07); HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.65); Normal sensitivity: U87MG. Δ EGFR cells vs. U87MG cells (D.R. 1.17)(Kueete et al., 2016c)
Futokadsurin B (lignan; 23)	<i>Lapaca togensis</i> Pax (Euphorbiaceae) (Kueete et al., 2015e)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{-/-}$) cells, HepG2 cells (Kueete et al., 2015e)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R.0.36); HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. <0.37) (Kueete et al., 2016e); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.1.14) (Kueete et al., 2015e)
Gancaonin Q (flavonoid; 24)	<i>Dorstenia angusticornis</i> Engl. (Kueete et al., 2007b)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, PF-382 cells, HL-60 cells, MiaPaCa-2 cells, Capan-1 cells, MCF-7 cells, SW-680 cells, 786-0 cells, U87MG cells, Colo-38 cells, HeLa cells, Caski cells (Kueete et al., 2011b)	Induces apoptosis in CORF-CEM cells via caspase 3/7 activation; anti-angiogenic effect via inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs (Kueete et al., 2011b)
Guieraone A (naphthyl butenone; 25)	<i>Guiera senegalensis</i> J. F. Gmel (Combretaceae) (Kueete et al., 2012)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, PF-382 cells, MiaPaCa-2 cells, Capan-1 cells, MCF-7 cells, 786-0 cells, U87MG cells, A549 cells, Colo-38 cells, HeLa cells, Caski cells (Kueete et al., 2012), THP-1 cells (Flot et al., 2006)	Showned anti-angiogenic activity via the inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail embryo; induces apoptosis in CORF-CEM and cell cycle arrest; affects the regulation of several pathways in CORF-CEM cells such as the Cell Cycle, G2/M DNA Damage Checkpoint Regulation and ATM Signaling pathways (Kueete et al., 2012)
Gutiferone E (benzophenone; 26)	<i>Garcinia punctata</i> Oliv. (Guttiferae) (Kueete et al., 2013d)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2013d); HT29 cells (Einbond et al., 2013) and SW-480 (Baggett et al., 2005; Protiva et al., 2008)	Hypersensitivity: HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.62); U87MG. Δ EGFR cells vs. U87MG cells (D.R. 0.43); Normal sensitivity: HL60AR cells vs. HL60 cells (D.R. 1.00); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.1.19); induces apoptosis in HCT116, HT29 and SW480 cells through loss MMP and caspase 3/7 activation (Protiva et al., 2008); induces apoptosis in CORF-CEM cells via activation of initiator caspases 8 and 9 and effector caspase 3/7 as well as loss of MMP (Kueete et al., 2013d); induces apoptosis in HeLa cells (Liu et al., 2010)
Isobavachalcone (flavonoid; 27)	<i>Dorstenia barteri</i> Bureau var. <i>multiradiata</i> (Moraceae) (Mbaveng et al., 2008; Kueete and Sandjo, 2012)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2015c); OVCAR-8 cells, MCF-7 cells and A549 cells (Jing et al., 2010; Kueete and Sandjo, 2012)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.13); HCT116 ($\rho 53^{-/-}$) cells vs. HCT116 ($\rho 53^{+/+}$) cells (D.R. 0.84); U87MG. Δ EGFR cells vs. U87MG cells (D.R. 0.73); induces apoptosis in IMR-32 and NB-39 cells via activation of caspases-3 and -9 and Bax upregulation (Nishimura et al., 2007); inhibits matrix metalloproteinases-2 secretion in U87 cells (Ngameni et al., 2007); induces apoptosis in CORF-CEM cells, mediated by caspase 3/7, 8 and 9 activation, the disruption of MMP and increase ROS production (Kueete et al., 2015c)
Isogarcinol (benzophenone; 28)	<i>Hypericum lanceolatum</i> Lam. (Hypericaceae) (Kueete et al., 2013d; Pieme et al., 2015). <i>Garcinia ovalifolia</i> (Pieme et al., 2015)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 ($\rho 53^{+/+}$) cells, HCT116 ($\rho 53^{-/-}$) cells, U87MG cells, U87MG. Δ EGFR cells, HepG2 cells (Kueete et al., 2013d); HL60 cells (Pieme et al., 2015)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.31); U87MG. Δ EGFR cells vs. U87MG cells (D.R. 0.83); Normal sensitivity: HL60AR cells vs. HL60 cells (D.R. 1.02) (Kueete et al., 2013d); induces G2/S cycle arrest and apoptosis in HL60 cells through MMP loss (Pieme et al., 2015)

(Continued)

TABLE 2 | Continued

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
Isoneocauterol (isoflavonoid; 29)	<i>Erythrina excelisa</i> Baker (Fabaceae) (Kueite et al., 2014c)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014d); H4IIE cells (Wafjien et al., 2007).	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.17); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.78); Normal sensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.93); induces apoptosis in CCRF-CEM cells via the activation of caspases 8 and 9 and caspase 3/7; loss of MMP and increase ROS production (Kueite et al., 2014c)
Isoxanthohymol (benzophenone; 30)	<i>Garcinia punctata</i> Oliv.(Guttiferae) (Kueite et al., 2013d)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2013c) and SW-480 (Bagggett et al., 2005)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.54); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.49); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 1.08); HL60AR cells vs. HL60 cells (D.R. 1.00); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 1.12); induces apoptosis in CCRF-CEM cells via activation of initiator caspases 8 and 9 and effector caspase 3/7 as well as loss of MMP (Kueite et al., 2013d); induces apoptosis in HeLa cells (Liu et al., 2010).
Laburnetin (flavonoid; 32)	<i>Ficus chlamydocarpa</i> Midbr. & Burret (Moraceae) (Kueite et al., 2008)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2016c); UMR106 cells (Maoli et al., 2006)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.74); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.86) (Kueite et al., 2016c); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R.0.98) (Kueite et al., 2016c)
Morusigin I (xanthone; 33)	<i>Garcinia nobilis</i> Engl. (Guttiferae) (Foutsisa et al., 2012, 2013)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2013b)	Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 1.03) (Kueite et al., 2013b)
Naringenin (flavonoid; 34)	<i>Aframomum arundinaceum</i> (Oliver & Harbury) K. Schum (Zingiberaceae)(Kueite et al., 2014a)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014a)	Hypersensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 0.64); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.60); HepG2 cells vs. AML12 cells (D.R. <0.59); Normal sensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 cells (p53 ^{+/+}) (D.R. 1.02)(Kueite et al., 2014a); induces apoptosis in HepG2 cells and DLD-1 cells through caspase-3 activation and poly(ADP-ribose) polymerase cleavage (Itoita et al., 2004); induces apoptosis in HL60 cells through activation of NF-kappaB and necrosis involving the loss of ATP (Kanno et al., 2006); induces apoptosis in THP-1 cells through downregulation of Akt and caspase-3 activation (Park et al., 2008); up-regulates the expression of death receptor 5 and enhances TRAIL-induced apoptosis in A549 cells (Jin et al., 2011)
Neobavaisoflavone (isoflavonoid; 35)	<i>Erythrina sonnegalensis</i> DC (Fabaceae) (Kueite et al., 2014c)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014d); LNCaP cells (Szliszka et al., 2011).	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.87); U87MG.ΔEGFR cells vs. U87MG cells (D.R. <0.58); Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R.1.20) (Kueite et al., 2014c); induces apoptosis via the inhibition of metastasis in U873MG cells (Kim et al., 2014); induces TRAIL-mediated apoptosis in LNCaP cells (Szliszka et al., 2011)
Neocyclomorusin (flavonoid; 36)	<i>Erythrina sigmoidea</i> Hua (Leguminosae) (Kueite et al., 2014c)	Cytotoxicity toward CCRF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, HCT116 (p53 ^{+/+}) cells, U87MG cells, U87MG.ΔEGFR cells (Kueite et al., 2014c)	Normal sensitivity: CEM/ADR5000 cells vs. CCRF-CEM cells (D.R. 1.19) (Kueite et al., 2014c)
Plumbagin (naphthoquinone; 37)	<i>Plumbago dawei</i> (Maniatiu et al., 2009); <i>Plumbago zeylanica</i> ; (Kueite et al., 2016d); <i>Diospyros crassiflora</i> and <i>Diospyros canaliculata</i> (Kueite and Efferth, 2011)	Cytotoxicity toward A549 cells, SPC212 cells; DLD-1 cells, Caco2 cells; MCF-7 cells (Kueite et al., 2016d)	Induces ROS-mediated apoptosis, release of mitochondrial cytochrome c and activation of caspase-3 and -9 in ME-180 cells (Srinivas et al., 2004); induces apoptosis in MCF-7 cells mediated by increase ROS production and MMP loss (Kueite et al., 2016d); DNA: Methylation of CpG sites) -47.48.49 - in ARHGEF12 (Kueite and Efferth, 2011); inhibits the NF-kappaB activation pathway in cancer cells leading to suppression of NF-kappaB-regulated gene products (Sandur et al., 2006); induces apoptosis and cell cycle arrest in A549 cells through p53 accumulation via c-Jun NH2-terminal kinase-mediated phosphorylation (Hsu et al., 2008); induces apoptosis in MDA-MB-231 and MCF-7 cells via inactivation of NF-kB and Bcl-2 (Ahmad et al., 2008); induces apoptosis in PC-3 cells, LNCaP cells and C4-2 cells through ROS generation, depletion of intracellular glutathione levels; reduces expression of superoxide dismutase 2 (Powolny and Singh, 2008); induces ROS-mediated apoptosis in NB4 cells <i>in vivo</i> (Xu and Lu, 2010)

(Continued)

TABLE 2 | Continued

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
Poinsettifolin B (flavonoid; 38)	<i>Dorstenia poinsettifolia</i> Engl. (Moraceae) (Ngajjui et al., 1999b)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015c)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.64); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 1.19); induces apoptosis in CORF-CEM cells via the disruption of MMP and increase ROS production (Kueite et al., 2015d)
Pycnanthulignone A (lignan; 39)	<i>Pycnanthus argoliensis</i> (Welw.) Ward (Myristicaceae) (Nono et al., 2010; Kueite et al., 2011c)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2016c)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.78); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.88); Normal sensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 1.02); induces apoptosis in CORF-CEM cells, mediated by loss of MMP and increase ROS production (Kueite et al., 2016c)
Pycnanthulignone B (lignan; 40)	<i>Pycnanthus argoliensis</i> (Welw.) Ward (Myristicaceae) (Nono et al., 2010; Kueite et al., 2011c)	Cytotoxicity toward CEM/ADR5000 cells (Kueite et al., 2016c)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. < 0.14) (Kueite et al., 2016c)
Kaempferol-3,7,4'-trimethylether (flavonoid; 31)	<i>Aframomum arundinaceum</i> (Oliver & Harbury) K. Schum (Zingiberaceae) (Kueite et al., 2014a)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells (Kueite et al., 2014a)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. < 0.83); HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. < 0.82); CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.99) (Kueite et al., 2014a)
Repanone (benzoquinone; 41)	<i>Maesa lanceolata</i> Forssk., <i>Myrsine Africana</i> L., <i>Embellia keniensis</i> R.E.Fr., <i>Embellia schimperii</i> Vaitke and <i>Rapanea pulchra</i> Gilg & Schellenb. (Ogweno Midlwo et al., 2002)	Cytotoxicity toward A549 cells, SPC212 cells; DLD-1, Caco2 cells; MCF-7 cells (Kueite et al., 2016b)	Induces apoptosis in MCF-7 cells mediated by increase ROS production and MMP loss (Kueite et al., 2016b)
Resveratrol β-D-glucopyranoside (stilbene; 42)	<i>Nauclea pobeguinii</i> (Pobég. ex Pellegr.) Merr. ex E.M.A. (Rubiaceae) (Kueite et al., 2015f)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015f)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.74); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.86); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.98) (Kueite et al., 2015f)
Sigmoidin H (isoflavonoid; 43)	<i>Erythrina senegalensis</i> DC (Fabaceae) (Kueite et al., 2014d)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, HCT116 (p53 ^{+/+}) cells, U87MG cells (Kueite et al., 2014d)	Normal sensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 1.02) (Kueite et al., 2014d)
Sigmoidin I (isoflavonoid; 44)	<i>Erythrina sigmoidea</i> Hua (Leguminosae) (Kueite et al., 2014c)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, U87MG cells, HepG2 cells (Kueite et al., 2014c)	Hypersensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 87); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.65); induces apoptosis in CORF-CEM cells via breakdown of MMP and increase in ROS production (Kueite et al., 2014c)
Sophorapterocarpan A (isoflavonoid; 45)	<i>Erythrina sigmoidea</i> Hua (Leguminosae) (Kueite et al., 2014c)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ^{+/+}) cells, HCT116 (p53 ^{-/-}) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2014c)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.90); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.69); Normal sensitivity: HCT116 (p53 ^{-/-}) cells vs. HCT116 (p53 ^{+/+}) cells (D.R. 0.95); induces apoptosis in CORF-CEM cells via breakdown of MMP and increase in ROS production (Kueite et al., 2014c)
Xanthone Y ₁ (xanthone; 46)	<i>Vismia laurentii</i> De Wild. (Guttiferae) (Waboo et al., 2007)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, HL-60 cells, MIA-PaCa-2 cells, MCF-7 cells, SW-680 cells, 786-O cells, U87MG cells, A549 cells, Colo-38 cells, HeLa cells, Caski cells (Kueite et al., 2011d)	Anti-angiogenic effects through inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs; induces apoptosis and cell cycle arrest in S-phase in CORF-CEM cells mediated by Caspase 3/7 activation (Kueite et al., 2011d)

(Continued)

TABLE 2 | Continued

Classes and compounds	Plant sources	Reported cytotoxic activity ^a	Molecular targets and/or effects on resistant cells
ALKALOIDS			
1,3-dimethoxy-10-methylacridone (acridone); 47	<i>Orica suaveolens</i> Engl. (Rutaceae) (Foujisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015b)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.33); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.51); Normal sensitivity: HCT116 (p53 ⁻ /-) cells vs. HCT116 (p53 ⁺ /+) cells (D.R. 0.97); induces apoptosis in CORF-CEM cells, mediated by ROS production. (Kueite et al., 2015b)
1-hydroxy-3-methoxy-10-methylacridone (acridone); 48	<i>Orica suaveolens</i> Engl. (Rutaceae) (Foujisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015b)	Hypersensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.18); HCT116 (p53 ⁻ /-) cells vs. HCT116 (p53 ⁺ /+) cells (D.R. 0.39); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.21) (Kueite et al., 2015b)
Arbormine (acridone); 49	<i>Uapaca togensis</i> Pax (Euphorbiaceae) (Kueite et al., 2015e)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015e)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.11); MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.87); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.34); induces apoptosis in CORF-CEM cells (Kueite et al., 2015e)
Evoxanthine (acridone); 50	<i>Orica suaveolens</i> Engl. (Rutaceae) (Foujisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015b)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.45) (Kueite et al., 2015b)
Isoterandrine (isoquinoline); 51	<i>Xylopia aethiopia</i> (Dunal) A. Rich. (Annonaceae) (Kueite et al., 2015g)	Cytotoxicity toward CORF-CEM cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015g)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.38); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 0.92); induces apoptosis in CORF-CEM cells, mediated by ROS production (Kueite et al., 2015g)
Montrifoline 52	<i>Orica suaveolens</i> Engl. (Rutaceae) (Foujisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> cells, MDA-MB-231- <i>BCRP</i> cells, HCT116 (p53 ⁺ /+) cells, HCT116 (p53 ⁻ /-) cells, U87MG cells, U87MG.ΔEGFR cells, HepG2 cells (Kueite et al., 2015b)	Hypersensitivity: U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.74) (Kueite et al., 2015b)
Noreoxanthine (acridone); 53	<i>Orica suaveolens</i> Engl. (Rutaceae) (Foujisa et al., 2013)	Cytotoxicity toward CORF-CEM cells, CEM/ADR5000 cells, MDA-MB-231- <i>pcDNA</i> , MDA-MB-231- <i>BCRP</i> , HCT116 (p53 ⁺ /+), HCT116 (p53 ⁻ /-), U87MG, U87MG.ΔEGFR, HepG2 (Kueite et al., 2015b)	Hypersensitivity: CEM/ADR5000 cells vs. CORF-CEM cells (D.R. 0.75); U87MG.ΔEGFR cells vs. U87MG cells (D.R. 0.06); Normal sensitivity: MDA-MB-231- <i>BCRP</i> cells vs. MDA-MB-231- <i>pcDNA</i> cells (D.R. 1.17) (Kueite et al., 2015b)

^aReported cell lines: leukemia cells [CORF-CEM, CEM/ADR5000, HL60, and HL60AR; NB4 cells; PF-382 cells; CEM-SS cells, THP-1 cells]; Carcinoma cells [MDA-MB-231-*pcDNA*3, MDA-MB-231-*BCRP* clone 23, and MCF-7 breast cancer cells; HT29, SW-480, SW-680, HCT116 (p53⁺/+), and HCT116 (p53⁻/-)] colon cancer cells; U373MG, U87MG, and U87MG.ΔEGFR glioblastoma cells; HepG2; hepatocarcinoma; IMR-32 and NB-39 human neuroblastoma cells; AML12; normal hepatocytes; A549 human non-small cell lung cancer (NSCLC) cells, SPC212 human mesothelioma cells; H2T08 and H1289 lung cancer cells; DLD-1 and Caco2 colorectal adenocarcinoma cells; CaOV3 and OVCAR-8 ovarian carcinoma cells; C4-2, MiaPaca-2, Capan-1 and PC-3 pancreatic carcinoma cells, LNCaP human prostatic adenocarcinoma cells; ME-180, SiHa, Caski and HeLa cervical carcinoma cells; B16F-10 and Colo-38 skin melanoma cells; H4IIE rat hepatoma cells; UMRI106 rat osteogenic sarcoma cells; D.R., degree of resistance; D.R. is determined as the ratio of IC₅₀ value in the resistant divided by the IC₅₀ in the sensitive cell line; AML12, HL60AR, CEM/ADR5000, MDA-MB-231-*BCRP*, HCT116 (p53⁻/-) and U87MG.ΔEGFR were used as the corresponding resistant counterpart for HepG2, HL60, CORF-CEM, MDA-MB-231-*pcDNA*, HCT116 (p53⁺/+), U87MG, respectively; Hypersensitivity, D.R. < 1; Normal sensitivity, D.R. equal of around 1; MMP, mitochondrial membrane potential; ROS, reactive oxygen species.

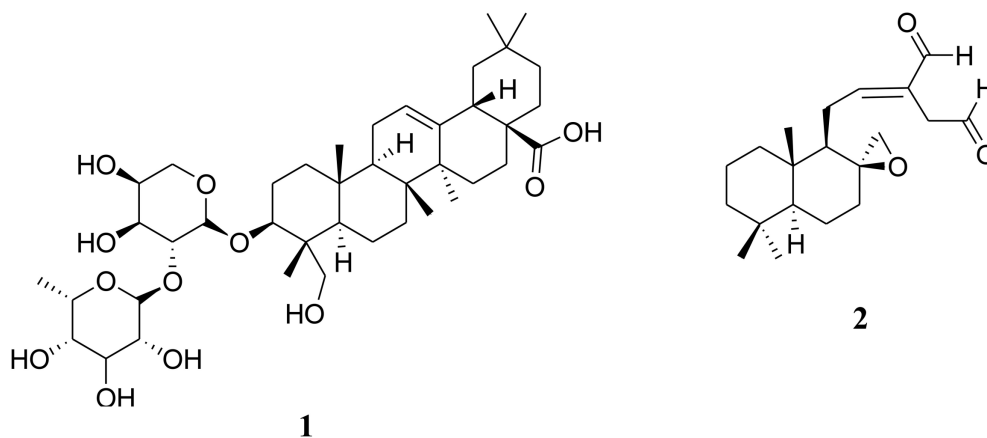


FIGURE 1 | Chemical structures of two cytotoxic terpenoids [α -hederin (**1**) and galanal A (**2**)] isolated from Central, East and West African plants.

Welw C.C. Berg. (Kuete et al., 2013b) and xanthone V₁ (**46**) from *Vismia laurentii* De Wild. (Kuete et al., 2011d). Activators of initiator caspases 8 and 9 include benzophenone **26** (Kuete et al., 2013d) and **30** (Kuete et al., 2013d), flavonoid **18** (Kuete et al., 2015c), isoflavonoid **9** (Kuete et al., 2014c), or xanthone **17** (Kuete et al., 2013b).

Plants and Derived Compounds Targeting the Mitochondria of Cancer Cells

Several crude extracts and isolated compounds from CEWA plants targeted mitochondria to induce apoptosis in cancer cells (Tables 1, 2). Plant extracts inducing MMP alterations include: the Annonaceae plants *Annona muricata* Lin. (Kuete et al., 2016b), *Anonidium mannii* (oliv) Engl. et Diels. (Kuete et al., 2013a) and *Xylopiya aethiopicum* (Dunal) A. Rich. (Kuete et al., 2013c), a plant of Araliaceae family, *Polyscias fulva* (Hiern) Harms. (Kuete et al., 2014e), of Bignoniaceae, *Markhamia tomentosa* (Benth.) K.Schumex.Engl. (Ibrahim et al., 2013), of Compositae, *Echinops giganteus* var. *leyli* (C. D. Adams) A. Rich. (Kuete et al., 2013c), the Euphorbiaceae, *Alchornea cordifolia* (Schum. & Thonn.) Müll.-Arg. (Kuete et al., 2016e) and *Uapaca togoensis* Pax. (Kuete et al., 2015e), the Fabaceae, *Albizia adianthifolia* (Schum.) (Kuete et al., 2016e) and *Erythrina sigmoidea* Hua (Kuete et al., 2016a), the Moraceae, *Dorstenia psilurus* Welwitsch (Pieme et al., 2013), the Passifloraceae, *Passiflora edulis* Sims (Kuete et al., 2016b), the Piperaceae, *Piper capense* L.f. (Kuete et al., 2013c), the Poaceae, *Imperata cylindrica* Beauv. var. *koenigii* Durand et Schinz (Kuete et al., 2013c) and the Rutaceae, *Vepris soyauxii* Engl. (Kuete et al., 2013a). Several molecules isolated from plants of CEWA also targeted mitochondria. Some of them include: anthraquinones, damnacanthol (**19**) and damnacanthol (**20**) from *Pentas schimperi* (Hook. f.) Verde (Kuete et al., 2015a), the benzoquinone, rapanone (**41**) from *Maesa lanceolata* Forssk., *Myrsine africana* L., *Embelia keniensis* R.E.Fr., *Embelia schimperi* Vatke and *Rapanea pulchra* Gilg & Schellenb. and the naphthoquinone, plumbagin (**37**) from *Plumbago* and *Diospyros* species (Kuete et al., 2016d), benzophenones, **26**

and **30** (Kuete et al., 2013d), flavonoids, 3,4',5-trihydroxy-6'',6''-dimethylpyrano[2,3-g]flavone (**5**) isolated *Xylopiya aethiopicum* (Dunal) A. Rich. (Kuete et al., 2015g), 4'-hydroxy-2',6'-dimethoxychalcone (**6**) from *Polygonum limbatum* Meisn (Kuete et al., 2014b), abyssinone IV (**11**) from *Erythrina sigmoidea* Hua (Kuete et al., 2014c), alpinumisoflavone (**12**) from *Ficus chlamydocarpa* Mildbr. & Burret (Kuete et al., 2014c), dorsmanin F (**21**) from *Dorstenia mannii* Hook.f. (Kuete et al., 2015d), compound **27** (Kuete et al., 2015c) and poinsettifolin B (**38**) from *Dorstenia poinsettifolia* Engl. (Kuete et al., 2015d), isoflavonoids, 6 α -hydroxyphaseollidin (**9**) (Kuete et al., 2014c), isoneorautenol (**29**) (Kuete et al., 2014d), sigmoidin I (**44**) and sophorapterocarpan A (**45**) (Kuete et al., 2014c) from *Erythrina sigmoidea* Hua, a lignan, pycnanthulignene A (**39**) from *Pycnanthus angolensis* (Welw.) Ward (Kuete et al., 2016c) and a xanthone, cudraxanthone I (**17**) from *Milicia excelsa* Welw C.C. Berg. (Kuete et al., 2013b).

Plants and Derived Compounds Inducing ROS Increase in Cancer Cells

The induction of apoptosis in cancer cells by some plants and derived molecules of CEWA was due to induced-ROS increase (Tables 1, 2). Plants that exert their anticancer activities via this mechanism include: *Alchornea cordifolia* (Schum. & Thonn.) Müll.-Arg. (Kuete et al., 2016e), *Anonidium mannii* (oliv) Engl. et Diels. (Kuete et al., 2013a), *Dorstenia psilurus* Welwitsch (Pieme et al., 2013), *Piper capense* L.f. (Kuete et al., 2013c), *Polyscias fulva* (Hiern) Harms. (Kuete et al., 2014e), *Sclerocarya birrea* (A. Rich.) Hochst (Anacardiaceae) (Armentano et al., 2015). Compounds inducing increase in ROS production include: acridone alkaloid 1,3-dimethoxy-10-methylacridone (**47**) and isoquinoline alkaloid isotetrandrine (**51**), anthraquinones **19** and **20** (Kuete et al., 2015a), benzoquinone **41** (Kuete et al., 2016d) and naphthoquinone **37** (Kuete et al., 2016d), flavonoids **6** (Kuete et al., 2014b), **11** (Kuete et al., 2014c), **12** (Kuete et al., 2016c), **27** (Kuete et al., 2015c), **38** (Kuete et al., 2015d), isoflavonoids **9** (Kuete et al., 2014c), **29** (Kuete et al., 2014d), **44** and **45** (Kuete et al., 2014c), and lignan **39** (Kuete et al., 2016c).

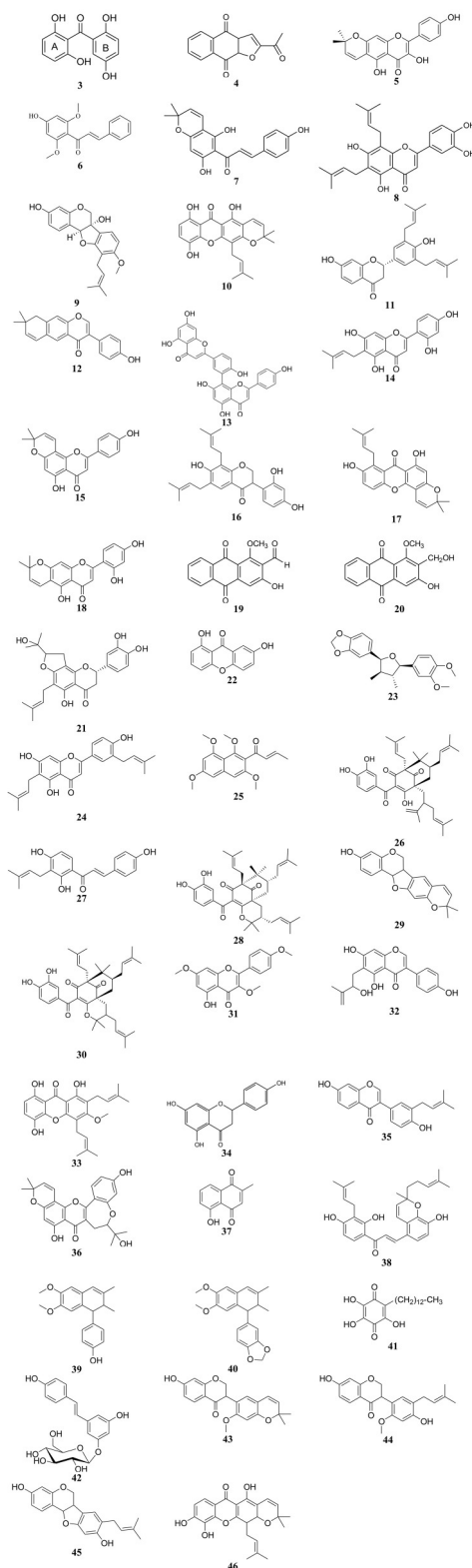


FIGURE 2 | Chemical structures of hit cytotoxic phenolics isolated from Central, East and West African plants. 2,2',5,6'-tetrahydroxybenzophenone (Continued)

FIGURE 2 | Continued

(3); 2-acetylfuro-1,4-naphthoquinone (4); 3,4',5-trihydroxy-6'',6''-dimethylpyrano[2,3-g]flavone (5); 4'-hydroxy-2',6'-dimethoxychalcone (6); 4-hydroxylonchocarpin (7); 6,8-diprenyleriodictyol (8); 6 α -hydroxyphaseollidin (9); 8-hydroxycudraxanthone G (10); abyssinone IV (11); alpinumisoflavone (12); armentoflavone (13); artocarpesin (14); atalantoflavone (15); bidwillon A (16); cudraxanthone I (17); cycloartocarpesin (18); damnacanthal (19); damnacanthol (20); dorsmanin F (21); euxanthone (22); futokadsurin B (23); gancaonin Q (24); guieranone A (25); guttiferone E (26); isobavachalcone (27); isogarcinol (28); isoneorautenol (29); isoxanthochymol (30); kaempferol-3,7,4'-trimethylether (31); laburnetin (32); morusignin I (33); naringenin (34); neobavaisoflavone (35); neocyclomorusin (36); plumbagin (37); poinsettifolin B (38); pycnanthulignene A (39); pycnanthulignene B (40); rapanone (41); resveratrol β -D-glucopyranoside (42); sigmoidin H (43); sigmoidin I (44); sophorapterocarpin A (45); xanthone V₁ (46).

Angiogenesis

Angiogenesis as treatment target against cancer was merely studied for botanicals from Africa. The Fabaceae *Calliandra portoricensis* (Jacq.) (Adaramoye et al., 2015) was reported as angiogenesis inhibitor through inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs. Compounds with similar effects include naphthoquinone 2-acetylfuro-1,4-naphthoquinone (4) (Kuate et al., 2011d), flavonoids 7, 8, and 24 (Kuate et al., 2011b), the naphthyl butenone guieranone A (25) and the xanthone 46 (Kuate et al., 2011d).

African Plants and Compounds with Regular Sensitivity and Collateral Sensitivity in Drug Resistant Cancer Cells

The investigation of the mode of action of botanicals and phytochemicals from the flora of Africa is not yet done in a systematic manner due to the lack of facilities and appropriate technology in research centers throughout the continent. However, the fight against MDR in cancer will provide conceptual clues on the molecular targets of the active samples. In collaborations with more equipped research institutes in Western countries, plants and isolated compounds from the flora of CEWA were tested on cancer cells expressing well-known drug resistance phenotypes. In **Tables 1, 2**, results on samples are documented, that inhibited resistant cell lines with similar efficacy than sensitive ones (regular sensitivity). In some cases, it was observed that resistant cells were killed with even better efficacy than sensitive cells (hyper-sensitivity or collateral sensitivity). These plant extracts and phytochemicals could be especially useful to fight MDR in cancer. In this section, we will focus on plants and compounds exerting hypersensitivity on cell lines over-expressing ABC transporters, EGFR and with p53 knock out genes.

Plants and Compounds Acting in Cancer Cells Over-Expressing ABC Transporters

Some botanicals and phytochemicals from CEWA were screened against ABC transporters-expressing cell lines. The most investigated cell lines included the P-gp-overexpressing

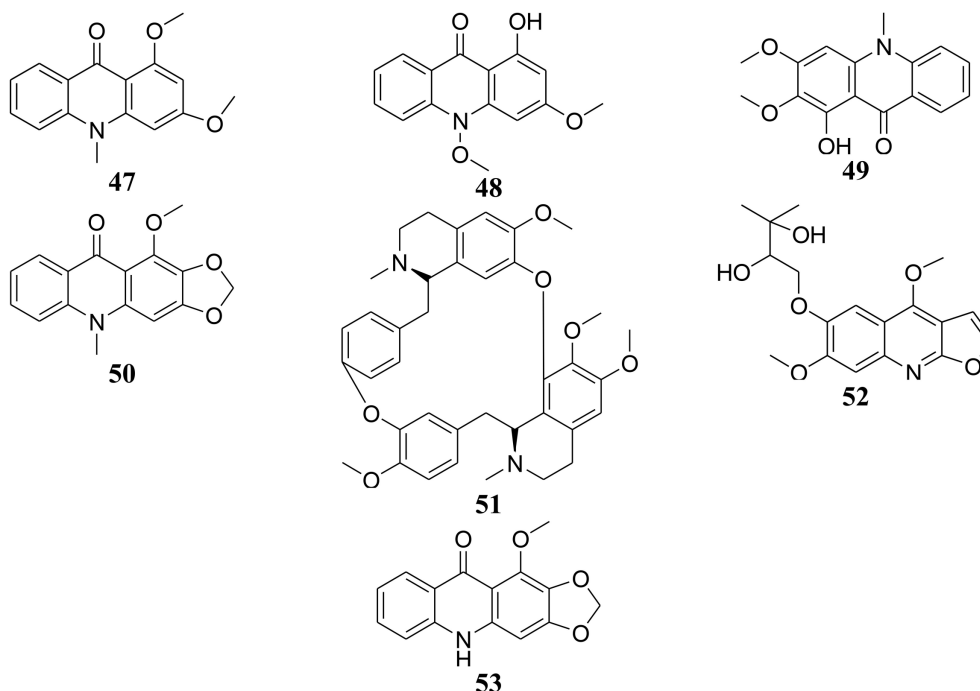


FIGURE 3 | Chemical structures of hit cytotoxic alkaloids isolated from plants of Central, East and West Africa. 1,3-dimethoxy-10-methylacridone (**47**); 1-hydroxy-3-methoxy-10-methylacridone (**48**); arborinin (**49**); evoxanthine (**50**); isotetrandrine (**51**); monrifoline (**52**); norevioxanthine (**53**).

CEM/ADR5000 leukemia cell line, the MRP1-expressing HL60/AR leukemia cell line and BCRP-expressing MDA-MB-231/BCRP breast adenocarcinoma cell line. The studies were mainly conducted by the team of Professor Thomas Efferth (University of Mainz, Germany). Plants and compounds inducing hypersensitivity in these cell lines are summarized in **Tables 1, 2**.

The hypersensitivity of CEM/ADR5000 cells compared to its parental cell line CCRF-CEM was induced by *Aframomum arundinaceum* (Oliver & Hanbury) K. Schum (Zingiberaceae) (Kвете et al., 2014a), *Imperata cylindrica* Beauv. var. *koenigii* Durand et Schinz (Poaceae) (Kвете et al., 2013c), *Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A. (Rubiaceae) (Kвете et al., 2015f), *Pachypodanthium staudtii* Engl & Diels (Annonaceae) (Kвете et al., 2016b), *Piper capense* L.f. (Piperaceae) (Kвете et al., 2013c) and *Zinziber officinale Roscoe* (Zingiberaceae) (Kвете et al., 2011a). Compounds with similar activity included: acridone alkaloids, **49** and **53** (Kвете et al., 2015b), anthraquinone, **19** (Kвете et al., 2015a), flavonoids, 4'-hydroxy-2',6'-dimethoxychalcone (**6**) from *Polygonum limbatum* Meisn (Kвете et al., 2014b), **12** (Kвете et al., 2016c), amentoflavone (**13**) from *Dorstenia barteri* (Kвете et al., 2016c), atalantoflavone (**15**) from *Erythrina sigmoidea* Hua (Kвете et al., 2014c), naringenin (**34**) from *Aframomum arundinaceum* (Oliver & Hanbury) K. Schum (Kвете et al., 2014a), lignans, futokadsurin B (**23**) from *Uapaca togoensis* Pax. (Kвете et al., 2016c), **39** and **40** (Kвете et al., 2016c) and xanthone **17** (Kвете et al., 2013b).

Plant extracts inducing hypersensitivity in MDA-MB-231-BCRP clone 23 cells compared to its sensitive counterparts MDA-MB-231 cells include: *Aframomum polyanthum* K. Schum (Zingiberaceae) (Kвете et al., 2014a), *Nauclea latifolia* Smith. (Rubiaceae) (Kвете et al., 2014a), *Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A. (Kвете et al., 2015f), *Pachypodanthium staudtii* Engl & Diels (Kвете et al., 2016b) and *Uapaca togoensis* Pax. (Euphorbiaceae) (Kвете et al., 2015e) (**Table 1**). Compounds exerting similar activity included: alkaloids, **47**, **48**, and **49** (Kвете et al., 2015b), diterpene, galanal A (**2**) isolated from *Aframomum arundinaceum* (Oliver & Hanbury) K. Schum (Kвете et al., 2014a), benzophenone, isogarcinol (**28**) from *Hypericum lanceolatum* Lam. (Kвете et al., 2013d), **30** (Kвете et al., 2013d), anthraquinones, **19** and **20** (Kвете et al., 2015a), flavonoids, **6** (Kвете et al., 2014b), **13** (Kвете et al., 2016c), **27** (Kвете et al., 2015c), kaempferol-3,7,4'-trimethylether (**31**) from *Aframomum arundinaceum* (Oliver & Hanbury) K. Schum (Kвете et al., 2014a), isoflavonoids, bidwillon A (**16**) from *Erythrina sigmoidea* Hua (Kвете et al., 2014c), **29** (Kвете et al., 2014d), **44** and **45** (Kвете et al., 2014c), lignan, **39** (Kвете et al., 2016c) and xanthones, 8-hydroxycudraxanthone G (**10**) from *Garcinia nobilis* Engl. (Kвете et al., 2013b), **17** (Kвете et al., 2013b) and euxanthone (**22**) (Kвете et al., 2016c).

Plants and Compounds Acting in EGFR Over-Expressing Cancer Cells

Several plants extracts and compounds were more active in the resistant glioblastoma U87MG.ΔEGFR cells than in its normal counterpart U87MG cells (D.R. < 0.90). They included: *Albizia*

adianthifolia (Schum.) and *Alchornea cordifolia* (Schum. & Thonn.) Müll.-Arg. (Kueete et al., 2016e), *Anonidium mannii* Engl. et Diels. (Anonaceae) (Kueete et al., 2013a), *Elaeophorbia drupifera* (Thonn.) Stapf. (Euphorbiaceae) (Kueete et al., 2013e), *Erythrina sigmoidea* Hua (Kueete et al., 2014a), *Gladiolus quartinianus* A. Rich. (Iridaceae) (Kueete et al., 2013a), *Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A. (Kueete et al., 2015f), *Vepris soyauxii* Engl. (Rutaceae) (Kueete et al., 2013a) and *Xylopia aethiopica* (Dunal) A.Rich. (Annonaceae) (Kueete et al., 2013c). Compounds with similar activity include: the alkaloids, **47–53** (Kueete et al., 2015b,g), anthraquinone, **19** (Kueete et al., 2015a), benzophenones, 2,2',5,6'-tetrahydroxybenzophenone (**3**) from *Hypericum lanceolatum* Lam. (Kueete et al., 2013d), **26** (Kueete et al., 2013d), **28** (Kueete et al., 2013d), **30** (Kueete et al., 2013d), flavonoids, **12** (Kueete et al., 2016c), dorsmanin F (**21**) (Kueete et al., 2015d), **27** (Kueete et al., 2015c), **34** (Kueete et al., 2014a), isoflavonoids, **16** (Kueete et al., 2014c), **35** (Kueete et al., 2014d), **44** and **45** (Kueete et al., 2014c), xanthenes, **10** (Kueete et al., 2013b), and **17** (Kueete et al., 2013b).

Plants and Compounds Acting in p53 Knockout Cancer Cells

Botanicals inducing hypersensitivity in p53 knockout cell line HCT116 ($p53^{-/-}$) compared to its sensitive counterpart HCT116 ($p53^{+/+}$) cell line included: *Beilschmiedia acuta* Kosterm (Lauraceae) (Kueete et al., 2014e), *Echinops giganteus* var. *lelyi* (C. D. Adams) A. Rich. (Compositae) (Kueete et al., 2013c), *Erythrina sigmoidea* Hua (Fabaceae) (Kueete et al., 2014a), *Nauclea latifolia* Smith. (Kueete et al., 2014a), *Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A. (Kueete et al., 2015f), *Polyscias fulva* (Hiern) Harms. (Araliaceae) (Kueete et al., 2014e) and *Uapaca togoensis* Pax. (Kueete et al., 2015e). Compounds acting in p53 knockout cancer cells included: alkaloid, **48** (Kueete et al., 2015b), benzophenone, **26** (Kueete et al., 2013d), flavonoids, **12** (Kueete et al., 2016c), **27** (Kueete et al., 2015c), laburnetin (**32**) (Kueete et al., 2016c), **38** (Kueete et al., 2015d), isoflavonoids, **9** (Kueete et al., 2014c), **11** (Kueete et al., 2014c), **16** (Kueete et al., 2014c), **29** (Kueete et al., 2014d), **44** (Kueete et al., 2014c), neobavaisoflavone (**35**) from *Erythrina senegalensis* DC (Kueete et al., 2014d), lignan, **23** (Kueete et al., 2016c), xanthenes, **10** (Kueete et al., 2013b), and **22** (Kueete et al., 2016c).

HIT CYTOTOXIC PLANTS OF CENTRAL, EAST AND WEST AFRICA

Some African plant extracts displayed very interesting cytotoxic effects with IC_{50} values below 20 $\mu\text{g/mL}$ in the majority of cancer cell lines tested. In this section, the synopsis of 10 strongest cytotoxic plants of CEWA as observed with *in vitro* screening assays is provided.

***Beilschmiedia acuta* Kosterm (Lauraceae)**

Beilschmiedia acuta [Synonyms: *Beilschmiedia acutifolia* (Engl. & K. Krause) Robyns & Wilczek or *Tylostemon acutifolius* Engl. & K. Krause] belongs to the family Lauraceae. The plant is mainly found in Cameroon and Central African Republic, where it is traditionally used to treat cancer and gastrointestinal infections

(Kueete et al., 2014e). The methanol extracts of leaves and roots of the plant were tested on a panel of cancer cell lines, including MDR phenotypes. Both leaves and roots extracts displayed good antiproliferative effects with respective IC_{50} values of 8.22 and 14.72 $\mu\text{g/mL}$ in leukemia CCRF-CEM cells, 19.76 and 26.74 $\mu\text{g/mL}$ in its resistant subline CEM/ADR5000 cells, 6.45 and 6.66 $\mu\text{g/mL}$ in breast adenocarcinoma MDA-MB-231 cells and 21.09 and 22.75 $\mu\text{g/mL}$ in its resistant counterparts MDA-MB-231/BCRP, 21.12 and 11.62 $\mu\text{g/mL}$ in colon adenocarcinoma HCT116 $p53^{+/+}$ and its resistant counterparts HCT116 $p53^{-/-}$, 7.46 and 7.27 $\mu\text{g/mL}$ in glioblastoma U87MG cells and its resistant counterparts U87MG. $\Delta EGFR$ cells and 23.09 $\mu\text{g/mL}$ for leaves extract in HepG2 cells (Kueete et al., 2014e). Interestingly, the two extracts were less toxic toward normal AML12 hepatocytes with IC_{50} values above 40 $\mu\text{g/mL}$ (Kueete et al., 2014e). Both leaves and roots extracts induced apoptosis in CCRF-CEM cells. However, the mode of induction of apoptosis was not detected when MMP and ROS production were investigated (Kueete et al., 2014e).

***Echinops giganteus* var. *lelyi* (C. D. Adams) A. Rich. (Compositae)**

Echinops giganteus a medicinal spicy plant of the family Compositae mainly found in Cameroon, Ethiopia, Rwanda, Sudan, Tanzania, Uganda, DR Congo. The plant is traditionally used to treat cancer, as well as heart and gastric troubles (Tene et al., 2004; Kueete et al., 2011a). The methanol extract of the rhizomes of the plant displayed good antiproliferative effects toward leukemia CCRF-CEM cells (IC_{50} : 6.68 $\mu\text{g/mL}$), CEM/ADR5000 cells (IC_{50} : 7.96 $\mu\text{g/mL}$) (Kueete et al., 2011a), HL60 cells (IC_{50} : 6.38 $\mu\text{g/mL}$) and HL60AR cells (IC_{50} : 9.24 $\mu\text{g/mL}$), MDA-MB-231-*pcDNA* cells (IC_{50} : 8.61 $\mu\text{g/mL}$), MDA-MB-231-BCRP cells (IC_{50} : 6.52 $\mu\text{g/mL}$), colon carcinoma HCT116 ($p53^{+/+}$) cells (IC_{50} : 3.58 $\mu\text{g/mL}$), HCT116 ($p53^{-/-}$) cells (IC_{50} : 3.29 $\mu\text{g/mL}$), glioblastoma U87MG cells (IC_{50} : 13.55 $\mu\text{g/mL}$) and U87MG. $\Delta EGFR$ cells (IC_{50} : 11.15 $\mu\text{g/mL}$), hepatocarcinoma HepG2 cells (IC_{50} : 14.32 $\mu\text{g/mL}$) (Kueete et al., 2013c). Importantly, this extract was less toxic to the normal human umbilical vein endothelial cells (HUVECs; IC_{50} > 80 $\mu\text{g/mL}$) (Kueete et al., 2011a) and to normal AML12 hepatocytes with less than 50% proliferation at 40 $\mu\text{g/mL}$ (Kueete et al., 2013c). This extract induced apoptosis in CCRF-CEM cells by loss of MMP (Kueete et al., 2013c).

***Erythrina Sigmoidea* Hua (Fabaceae)**

Erythrina sigmoidea (synonyms: *Erythrina dybowskii* Hua; *Erythrinaeriotricha* Harms; *Erythrina lanata* Taub. ex Gilg; *Erythrina sudanica* Baker f.) is a tree of 3–6 m, or 10–20 m belonging to the Fabaceae family. The plant is mainly found in Cameroon and Chad, where it is used as antidote (venomous stings, bites, etc.), diuretic, febrifuge and to treat arthritis, rheumatism, pulmonary troubles, stomach troubles, infectious diseases and kidney diseases (Burkill, 1985), gastrointestinal infections, venereal diseases and leprosy (Mabeku et al., 2011). The cytotoxic constituents of the plant include 6 α -hydroxyphaseollidin (**9**), atalantoflavone (**15**), bidwillon A (**16**), neobavaisoflavone (**35**), neocyclomorusin (**36**), and

sigmoidin I (44) (Kuetze et al., 2014c). The cytotoxicity of bark methanol extract was reported toward CCRF-CEM cells (IC₅₀: 18.50 μg/mL), CEM/ADR5000 cells (IC₅₀: 20.06 μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 22.37 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 27.42 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 19.63 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 16.22 μg/mL), U87MG cells (IC₅₀: 45 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 29.80 μg/mL), and HepG2 cells (IC₅₀: 22.34 μg/mL) (Kuetze et al., 2016a). This extract had low cytotoxicity toward normal AML12 hepatocytes, inducing less than 50% proliferation at 80 μg/mL (Kuetze et al., 2016a). It induced apoptosis in CCRF-CEM leukemia cells by disruption of the MMP (Kuetze et al., 2014a).

***Imperata cylindrica* Beauv. var. *koenigii* Durand et Schinz (Poaceae)**

Imperata cylindrica commonly known as cogon grass is a perennial rhizomatous grass of the Poaceae family. The plant is native to East and south East Asia, India, Micronesia, Melanesia, Australia, and Eastern and Southern Africa. In CEWA, the plant is found in Benin, Burkina Faso, Congo, Ivory Coast, Gambia, Ghana, Guinea, Kenya, Liberia, Mali, Mozambique, Niger, Nigeria, Senegal, Tanzania, Togo, Uganda. The plant is traditionally used as diuretic and anti-inflammatory agents and to treat cancer (Nishimoto et al., 1968; Kuetze et al., 2011a). The cytotoxicity of roots methanol extract of the plant was reported toward CCRF-CEM cells (IC₅₀: 8.4 μg/mL) and CEM/ADR5000 cells (IC₅₀: 7.18 μg/mL), pancreatic MiaPaca-2 cells (IC₅₀: 12.11 μg/mL) (Kuetze et al., 2011a), HL60 cells (IC₅₀: 7.94 μg/mL), HL60AR cells (IC₅₀: 30.60 μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 5.19 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 10.04 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 4.37 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 4.60 μg/mL), U87MG cells (IC₅₀: 19.99 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 10.68 μg/mL), and HepG2 cells (IC₅₀: 18.28 μg/mL) (Kuetze et al., 2013c). Less than 50% proliferation of CCRF-CEM cells was induced by this extract in normal AML12 hepatocytes (Kuetze et al., 2013c) meanwhile the IC₅₀ value as high as 47.73 μg/mL was obtained in HUVEC cells. This extract induced apoptosis in CCRF-CEM cells by loss of MMP (Kuetze et al., 2013c).

***Nauclea pobeguini* (Pobég. ex Pellegr.) Merr. ex E.M.A. (Rubiaceae)**

Nauclea pobeguini (synonym: *Sarcocephalus pobeguini* Pobég. ex Pellegr.) is a deciduous, small to medium-sized tree growing up to 30 m tall, sometimes a shrub. In CEWA, the plant is distributed in South Tropical Africa especially in Angola, Zambia, West Tropical Africa: Burkina, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Nigeria, Senegal, Sierra Leone, West-Central Tropical Africa: Cameroon, Central African Republic, Congo, DR Congo, Gabon. The plant is used in traditional medicine as abortive and to treat stomach ache and infectious diseases (Karou et al., 2011), jaundice (Kadiri et al., 2007), fever, diarrhea, worm, and malaria (Mesia et al., 2005). The cytotoxicity of the methanol extract from bark and leaves was reported toward CCRF-CEM cells (IC₅₀: 14.62 and 25.84 μg/mL, respectively), CEM/ADR5000 cells (IC₅₀: 11.56 and 25.55 μg/mL, respectively), HCT116

(*p53*^{+/+}) cells (IC₅₀: 16.19 and 32.72 μg/mL, respectively) and HCT116 (*p53*^{-/-}) cells (IC₅₀: 8.70 and 19.39 μg/mL, respectively) (Kuetze et al., 2015f). Resveratrol was identified as the major cytotoxic constituent of this extract (Kuetze et al., 2015f).

***Piper capense* L.f. (Piperaceae)**

Piper capense is a rather variable spicy plant ranging from a weakly erect, aromatic, evergreen shrub or subshrub, to a more or less herbaceous perennial and sometimes a straggling plant that scrambles into other plants for support. *Piper capense* is found from Guinea to Ethiopia, Angola and Mozambique. Traditionally, the plant is used as sleep inducing remedy, anthelmintic and to treat cancer (Kokowaro, 1976; Van Wyk and Gericke, 2000; Kuetze et al., 2011a). The cytotoxicity of seeds methanol extract was reported toward CCRF-CEM cells (IC₅₀: 7.03 μg/mL), CEM/ADR5000 (IC₅₀: 6.56 μg/mL) and MiaPaca-2 cells (IC₅₀: 8.92 μg/mL) (Kuetze et al., 2011a), HL60 cells (IC₅₀: μg/mL), HL60AR cells (IC₅₀: μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 4.17 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 19.45 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 4.64 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 4.62 μg/mL), U87MG cells (IC₅₀: 13.48 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 7.44 μg/mL), HepG2 cells (IC₅₀: 16.07 μg/mL) (Kuetze et al., 2013c). This extract was less toxic toward normal AML12 hepatocytes and HUVEC cells inducing less than 50% cell proliferation at 40 μg/mL and 80 μg/mL respectively (Kuetze et al., 2011a, 2013c). This extract induced apoptosis in CCRF-CEM cells by the loss of MMP and increase ROS production (Kuetze et al., 2013c).

***Polyscias fulva* (Hiern) Harms. (Araliaceae)**

Polyscias fulva is a deciduous to evergreen tree of the family Araliaceae. The plant is found in Tropical Africa, from Sierra Leone to Sudan, Ethiopia, and Yemen; in Angola, Zambia, Zimbabwe, and Mozambique. Traditionally, *Polyscias fulva* is used to treat malaria, fever, mental illness (Tshibangu et al., 2002), venereal infections and obesity (Jeruto et al., 2007; Focho et al., 2009), and cancer (Kuetze et al., 2014e). The phytochemical investigations of the plant led to the isolation of polysciasoside A, kalopanax-saponin B, α-hederin (Bedir et al., 2001; Kuetze and Efferth, 2011). Investigation of the cytotoxic potential of various parts of the plant demonstrated that the roots were more active than the leaves and bark (Kuetze et al., 2014e). Roots methanol extract had good cytotoxic effects on a panel of human cancer cell lines with the IC₅₀ values of 7.79 μg/mL (CCRF-CEM cells), 22.63 μg/mL (CEM/ADR5000 cells), 3.27 μg/mL (MDA-MB-231 cells), 16.67 μg/mL (MDA-MB-231/*BCRP* cells), 14.66 μg/mL (HCT116 *p53*^{+/+} cells), 5.98 μg/mL (HCT116 *p53*^{-/-} cells), 4.15 μg/mL (U87MG cells), 16.35 μg/mL (U87MG.Δ*EGFR* cells), and 12.99 μg/mL (HepG2 cells) (Kuetze et al., 2014e). Lower cytotoxicity of this extract was shown in normal AML12 hepatocytes with less than 50% cells proliferation at 40 μg/mL (Kuetze et al., 2014e). The active constituent of the plant was reported as α-hederin and this compound had moderate antiproliferative effects (IC₅₀ values ranged from 7.43 μM in CCRF-CEM cells to 43.98 μM in U87MG.Δ*EGFR* cells) against the above cancer cell lines (Kuetze et al., 2014e). The roots

methanol extract of *Polyscias fulva* induced apoptosis in CCRF-CEM cells, mediated by MMP alterations and increased ROS production (Kuetze et al., 2014e).

***Uapaca togoensis* Pax (Euphorbiaceae)**

Uapaca togoensis (Synonyms: *Uapaca chevalieri* Beille, *Uapaca guignardii* A. Chec. ex Beille, *Uapaca guineensis* sudanica (Beille) Hutch., *Uapaca perrottii* Beille *Uapaca somon* Aubrév. & Leandri) is an evergreen tree. The plant grows in tropical Africa, from Senegal to southern Chad and Central African Republic and from Gabon to DR Congo and northern Angola. In traditional medicine, the plant is used as antiemetic, lotion for skin disorders (Mengome et al., 2010), remedy for pneumonia, cough, fever, rheumatism, vomiting, epilepsy (Kone et al., 2006) and bacterial diseases (Kone et al., 2004). The cytotoxicity of the methanol extract from fruit was reported toward CCRF-CEM cells (IC₅₀: 4.23 μg/mL), CEM/ADR5000 cells (IC₅₀: 4.44 μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 25.85 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 4.17 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 3.69 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 3.09 μg/mL), U87MG cells (IC₅₀: 8.01 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 8.68 μg/mL), and HepG2 cells (IC₅₀: 19.90 μg/mL) (Kuetze et al., 2015e). This extract induced apoptosis in CCRF-CEM cells mediated by MMP loss (Kuetze et al., 2015e). The cytotoxic constituents of the extract were identified as a terpenoid, 11-oxo- α -amyril acetate, a lignan, futokadsurin B (**23**) and an alkaloid, arborinin (**49**) (Kuetze et al., 2015e).

***Vepris soyauxii* Engl. (Rutaceae)**

Vepris soyauxii (synonym: *Araliopsis soyauxii* Engl) is a plant of the family Rutaceae mostly found throughout West Africa, from Sierra Leone, Liberia, Ivory Coast, Mali, Ghana to Nigeria, and Cameroon. In traditional medicine, the plant is used as anti-fibriomyoma and to treat stomachache, malaria (Momeni et al., 2010) and cancer (Kuetze et al., 2013a). The antiproliferative effects of the methanol extract from leaves was reported toward CCRF-CEM cells (IC₅₀: 9.28 μg/mL), CEM/ADR5000 cells (IC₅₀: 11.72 μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 7.52 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 12.93 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 8.59 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 9.70 μg/mL), U87MG cells (IC₅₀: 8.75 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 4.09 μg/mL) and HepG2 cells (IC₅₀: 13.60 μg/mL) (Kuetze et al., 2013a). This extract induced apoptosis in CCRF-CEM cells mediated by disruption of MMP (Kuetze et al., 2013a). Besides, this extract had low cytotoxic effect toward normal AML12 hepacytes, inducing less than 50% proliferation at 40 μg/mL (Kuetze et al., 2013a).

***Xylopi aethiopica* (Dunal) A. Rich. (Annonaceae)**

Xylopi aethiopica is an aromatic tree of the family Annonaceae. The plant is native to the lowland rainforest and moist fringe forests in the savanna zones of Africa. The plant grows in Angola, Benin, Burkina Faso, Cameroon, Central African Republic, DR Congo, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Liberia, Mozambique, Nigeria, São Tomé and Príncipe, Senegal, Sierra Leone, Sudan, South Sudan,

Tanzania, Togo, and Uganda. Traditionally, this plant is used to treat cancer, constipation, uterine hemorrhage, fever and as diuretic (Iwu, 1993; Kuetze et al., 2011a; Okafor, 2012). The cytotoxicity of seeds methanol extract was demonstrated toward CCRF-CEM cells (IC₅₀: 3.91 μg/mL), CEM/ADR5000 cells (IC₅₀: 7.4 μg/mL) and Mia PaCa-2 cells (IC₅₀: 6.86 μg/mL) (Kuetze et al., 2011a), human cervical cancer cell line C-33A (IC₅₀: 30.8 μg/mL), breast adonocarcinoma MCF7 cells (IC₅₀: 60.2 μg/mL), human oral squamous carcinoma KB cells (IC₅₀: 62.5 μg/mL) (Adaramoye et al., 2011), HL60 cells (IC₅₀: 7.94 μg/mL), HL60AR cells (IC₅₀: 30.60 μg/mL), MDA-MB-231-*pcDNA* cells (IC₅₀: 5.19 μg/mL), MDA-MB-231-*BCRP* cells (IC₅₀: 10.04 μg/mL), HCT116 (*p53*^{+/+}) cells (IC₅₀: 4.37 μg/mL), HCT116 (*p53*^{-/-}) cells (IC₅₀: 4.60 μg/mL), U87MG cells (IC₅₀: 19.99 μg/mL), U87MG.Δ*EGFR* cells (IC₅₀: 10.68 μg/mL) and HepG2 cells (IC₅₀: 18.28 μg/mL) (Kuetze et al., 2013c). This extract was less toxic against AML12 hepatocytes and HUVEC cells inducing less than 50% cell proliferation at 40 and 80 μg/mL, respectively (Kuetze et al., 2011a, 2013c). Its also induced apoptosis in C-33A cells, nuclear fragmentation, cells accumulation in sub-G0/G1, cycle arrest in G2, up-regulation of p53 and p21 genes, and an increase in the Bax/Bcl-2 ratio (Adaramoye et al., 2011). It also induced apoptosis in CCRF-CEM cells by loss of MMP (Kuetze et al., 2013c). The cytotoxic constituents of this extract were identified as 16 α -hydroxy-entkauran-19-oic acid, 3,4',5-trihydroxy-6'',6''-dimethylpyrano[2,3-g]flavone, isotetrandrine (**51**) and *trans*-tiliroside (Kuetze et al., 2015g).

HIT CYTOTOXIC COMPOUNDS FROM PLANTS OF CENTRAL, EASTERN AND WESTERN AFRICA

Several bioactive constituents of African medicinal plants were identified. They include: terpenoids, phenolics and alkaloids (Table 2). However, phenolics were the best cytotoxic ingredients isolated from CEWA plants. In this section, a summary of the prominent antiproliferative phytochemicals identified in CEWA plant will be given.

Alkaloids

The isoquinoline alkaloid, isotetrandrine (**51**) isolated from *Xylopi aethiopica* was amongst the most active alkaloids reported in CEWA plants. This compound displayed interesting cytotoxic effects with IC₅₀ values below 10 μM toward a panel of sensitive and MDR cancer cell lines. These cell lines included: CCRF-CEM cells (IC₅₀: 1.53 μM), CEM/ADR5000 cells (IC₅₀: 2.36 μM), MDA-MB-231-*pcDNA* cells (IC₅₀: 7.28 μM), MDA-MB-231-*BCRP* cells (IC₅₀: 6.70 μM), HCT116 (*p53*^{+/+}) cells (IC₅₀: 2.39 μM), HCT116 (*p53*^{-/-}) cells (IC₅₀: 4.55 μM), U87MG cells (IC₅₀: 3.89 μM), U87MG.Δ*EGFR* cells (IC₅₀: 1.45 μM) and HepG2 cells (IC₅₀: 3.28 μM) (Kuetze et al., 2015g). Alkaloid, **51** was less toxic against the normal AML12 hepatocytes, inducing less than 50% proliferation at up to 64.27 μM (Kuetze et al., 2015g). This compound did not alter the integrity of the mitochondrial membrane in CCRF-CEM cells,

and its mode of induction of apoptosis was mainly by increased ROS production (Kueté et al., 2015g).

Phenolic Compounds

Phenolics have been so far the most represented group of secondary metabolites isolated from CEWA medicinal plants. Several compounds with interesting cytotoxic activities were identified within benzophenones, flavonoids and isoflavonoids, naphthyl butenone, quinones and xanthenes.

Benzophenones

Guttiferone E (**26**) and isoxanthochymol (**30**) isolated from *Garcinia punctata* Oliv. (Guttiferae) (Kueté et al., 2013d) showed good cytotoxic effects against a panel of human cancer cell lines. Compounds **26** and **30** have also been isolated from various *Garcinia* species such as *Garcinia pyrifera* (Roux et al., 2000), *Garcinia xanthochymus* (Baggett et al., 2005), *Garcinia virgata* (Merza et al., 2006), *Garcinia afzelii* (Lannang et al., 2010), *Garcinia livingstonei* (Yang et al., 2010), *Garcinia multiflora* (Liu et al., 2010) and from *Rheedia edulis* (Acuna et al., 2010). Compound **26** had an IC₅₀ value of 7.5 μM toward colon carcinoma SW-480 cells, meanwhile **30** was less active in this cell line (IC₅₀: 16.6 μM) (Baggett et al., 2005). Benzophenones **26** and **30** displayed good cytotoxic effects toward CCRF-CEM cells (IC₅₀: 6.86 and 9.55 μM, respectively), CEM/ADR5000 cells (IC₅₀: 13.57 and 10.33 μM, respectively), HL60 cells (IC₅₀: 11.69 and 8.92 μM, respectively), HL60AR cells (IC₅₀: 11.69 and 8.92 μM, respectively), MDA-MB-231-*pcDNA* cells (IC₅₀: 11.69 and 6.30 μM, respectively), MDA-MB-231-*BCRP* cells (IC₅₀: 13.92 and 3.42 μM, respectively), HCT116 (*p53*^{+/+}) cells (IC₅₀: 12.74 and 3.24 μM, respectively), HCT116 (*p53*^{-/-}) cells (IC₅₀: 7.87 and 3.62 μM, respectively), U87MG cells (IC₅₀: 7.87 and 6.40 μM, respectively), U87MG.Δ*EGFR* cells (IC₅₀: 3.39 and 3.12 μM, respectively) and HepG2 cells (IC₅₀: 11.13 and 8.34 μM, respectively) (Kueté et al., 2013d). Both **26** and **30** induced apoptosis in cervix adenocarcinoma HeLa cells (Liu et al., 2010). The two compounds also induced apoptosis in CCRF-CEM cells by activation of caspases 3/7, 8 and 9 and loss of MMP (Kueté et al., 2013d).

Flavonoids and Isoflavonoids

Flavonoids and isoflavonoids are amongst the most isolated and the most active phytochemicals identified in African medicinal plants (Kueté and Efferth, 2015). Well studied flavonoids from CEWA plants having prominent cytotoxic effect against human cancer cell lines include 4'-hydroxy-2',6'-dimethoxychalcone (**6**), isobavachalcone (**27**), neocyclomorusin (**36**), poinsettifolin B (**38**), 6α-hydroxyphaseollidin (**9**), isoneorautenol (**29**), neobavaisoflavone (**35**), sigmoidin I (**44**) and sophorapterocarpan A (**45**) (Table 2). Amongst them, isoflavonoid **9** revealed the best activity with IC₅₀ values below 10 μM on a panel of cancer cell lines including CCRF-CEM cells (IC₅₀: 3.36 μM), CEM/ADR5000 cells (IC₅₀: 5.51 μM), MDA-MB-231-*pcDNA* cells (IC₅₀: 5.70 μM), MDA-MB-231-*BCRP* cells (IC₅₀: 5.87 μM), HCT116 (*p53*^{+/+}) cells (IC₅₀: 5.68 μM), HCT116 (*p53*^{-/-}) cells (IC₅₀: 4.60 μM), U87MG cells (IC₅₀: 4.91 μM), U87MG.Δ*EGFR* cells (IC₅₀: 4.91 μM) and HepG2

cells (IC₅₀: 6.44 μM) (Kueté et al., 2014c). Compound **9** induced apoptosis in CCRF-CEM cells by the activation of caspases 3/7, 8 and 9 and breakdown of MMP as well as increased ROS production (Kueté et al., 2014c).

Naphthyl Butenone

Guieranone A (**25**), a major component of the leaves of *Guiera senegalensis* displayed good cytotoxic effects on a panel of human cancer cell lines. The cytotoxicity of **25** was documented toward CCRF-CEM cells (IC₅₀: 2.31 μM), CEM/ADR5000 cells (IC₅₀: 3.19 μM), MiaPaCa-2 cells (IC₅₀: 12.39 μM), Capan-1 cells (IC₅₀: 29.08 μM), MCF-7 cells (IC₅₀: 3.42 μM), 786-0 cells (IC₅₀: 11.32 μM), U87MG cells (IC₅₀: 7.78 μM), lung carcinoma A549 cells (IC₅₀: 2.28 μM), skin melanoma Colo-38 cells (IC₅₀: 7.69 μM), cervical carcinoma HeLa cells (IC₅₀: 1.61 μM), and Caski cells (IC₅₀: 3.73 μM) (Kueté et al., 2012) and leukemia THP-1 cells (IC₅₀: 13.43 μM) (Fiot et al., 2006). Compound **25** showed anti-angiogenic activity via the inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail embryo. It also induces apoptosis in CCRF-CEM cells. Meanwhile, microarray analysis demonstrated that it affected the regulation of several pathways in CCRF-CEM cells, including the cell cycle: G2/M DNA damage checkpoint regulation and ATM signaling pathways (Kueté et al., 2012).

Quinones

Two naphthoquinones isolated from African plants, 2-acetylfuro-1,4-naphthoquinone (**4**) and plumbagin (**37**), showed remarkable cytotoxic effects (Table 2). Compound **4** showed good cytotoxicity toward PF-382 cells (IC₅₀: 2.36 μM), MiaPaCa-2 cells (IC₅₀: 7.48 μM), MCF-7 cells (IC₅₀: 6.68 μM), U87MG cells (IC₅₀: 8.02 μM), Colo-38 cells (IC₅₀: 2.77 μM), HeLa cells (IC₅₀: 1.65 μM), and Caski cells (IC₅₀: 0.70 μM) (Kueté et al., 2011d). Naphthoquinone **4** revealed anti-angiogenic effects through inhibition of the growth of blood capillaries on the chorioallantoic membrane of quail eggs and also induced apoptosis and cell cycle arrest in S-phase in CCRF-CEM (Kueté et al., 2011d). The cytotoxic potential of compound **37** has widely been reported (Srinivas et al., 2004; Kuo et al., 2006; Powolny and Singh, 2008; Sun and McKallip, 2011; Kawiak et al., 2012). It has been isolated from various species of Plumbaginaceae, Ebenaceae and Droseraceae (Sagar et al., 2014). Compound **37** induced ROS mediated apoptosis in human cervical cancer ME-180 cells (Srinivas et al., 2004), human prostate cancer PC-3 cells and LNCaP cells (Powolny and Singh, 2008), G2-M arrest and autophagy by inhibiting the AKT/mammalian target of rapamycin (mTOR) pathway in MCF-7 cells and MDA-MD-231 cells (Kuo et al., 2006). Naphthoquinone **37** also induced apoptosis in Her2-overexpressing breast cancer cells through the mitochondrial-mediated pathway (Kawiak et al., 2012) as well as in human K562 leukemia cells through increased ROS and elevated tumor-necrosis-factor related apoptosis inducing ligand (TRAIL) receptor expression (Sun and McKallip, 2011).

Xanthenes

Xanthone V₁ (**46**) (Table 2) is one of the most active xanthenes with prominent cytotoxic effects isolated from CEWA plants,

displaying IC₅₀ values below or around 10 μM against MCF-7 cells (IC₅₀: 1.42 μM), 786-0 cells (IC₅₀: 9.62 μM), U87MG cells (IC₅₀: 9.64 μM), A549 cells (IC₅₀: 10.13 μM), Colo-38 cells (IC₅₀: 3.02 μM), HeLa cells (IC₅₀: 0.58 μM), and Caski cells (IC₅₀: 0.61 μM) (Kuetee et al., 2011d). This compound had anti-angiogenic effects, inhibiting the growth of blood capillaries on the chorioallantoic membrane of quail eggs. Compound **46** induced apoptosis and cell cycle arrest in S-phase in CCRF-CEM cells mediated by caspase 3/7 activation (Kuetee et al., 2011d).

CONCLUSION

The present review paper aimed at compiling and summarizing relevant data on the potential of medicinal plant and isolated natural products from Central, Eastern and Western Africa to combat cancer with emphasis on their possible cellular targets. This report could not deliver medical results on the therapeutic capacities of the flora of these three African Regions as anticancer drugs. Nonetheless, in phytochemical and pharmacological basic sciences it clearly shows that efforts are being made by African scientists and their international

collaborators to achieve this goal in the future. However, few research teams in the continent are already involved in the cytotoxic drug discovery from botanicals and it is expected that this review will stimulate other laboratories to undertake similar research projects to better valorize the African flora.

AUTHOR CONTRIBUTIONS

AM and VK wrote the manuscript; VK and TE designed and corrected the work. All authors read and approved the final version.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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