

Review Article

***In vitro* activities and mechanisms of action of anti-cancer molecules from African medicinal plants: a systematic review**

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Abstract: Cancer is one of the leading causes of death worldwide. In recent years, African countries have been faced with a rapid increase in morbidity and mortality due to this pathology. Management is often complicated by the high treatment costs, side effects and the increasing occurrence of resistance to treatments. The identification of new active ingredients extracted from endemic medicinal plants is definitively an interesting approach for the implementation of new therapeutic strategies: their extraction is often lower cost; their identification is based on an ethnobotanical history and a tradipratic approach; their use by low-income populations is simpler; this can help in the development of new synthetic molecules that are more active, more effective and with fewer side effects. The objective of this review is to document the molecules derived from African medicinal plants whose *in vitro* anti-cancer activities and the mechanisms of molecular actions have been identified. From the scientific databases *Science Direct*, PubMed and Google Scholar, we searched for publications on compounds isolated from African medicinal plants and having activity on cancer cells in culture. The data were analyzed in particular with regard to the cytotoxicity of the compounds and their mode of action. A total of 90 compounds of these African medicinal plants were selected. They come from nine chemical groups: alkaloids, flavonoids, polyphenols, quinones, saponins, steroids, terpenoids, xanthenes and organic sulfides. These compounds have been associated with several cellular effects: i) Cytotoxicity, including caspase activation, alteration of mitochondrial membrane potential, and/or induction of reactive oxygen species (ROS); ii) Anti-angiogenesis; iii) Anti-metastatic properties. This review points out that the cited African plants are rich in active ingredients with anticancer properties. It also stresses that screening of these anti-tumor active ingredients should be continued at the continental scale. Altogether, this work provides a rational basis for the selection of phytochemical compounds for use in clinical trials.

Keywords: Africa, cancer, phytochemicals, plants, molecular mechanisms

Introduction

Cancer can be defined as an irreversible change in cell homeostasis [1]. This pathology encompasses a range of malignant tumors characterized by rapid and uncontrolled growth of abnor-

mal cells and/or escape to programmed cell death or apoptosis. In advanced stages, cancer cells usually become metastatic, leaving their original primitive site after a phenomenon called epithelial-mesenchymal transition to invade other tissues and form new tumors [2].

Overall cancer survival statistics have improved in recent decades thanks to advances in diagnosis and prognosis, a better understanding of tumor biology, and most importantly, the implementation of new and more efficient treatments. However, the premature mortality rate from cancer has the highest incidence on the African continent due to a significant increase in new cases (more than one million) and especially deaths (more than 700,000) and with a more than doubling increase in new cases and deaths by 2040 [3]. Thus, cancer remains a real public health problem in Africa.

Conventional cancer treatment involve surgery to remove the tumor and followed by radiation therapy when the tumor is located [4]. After metastatic dissemination, cancer chemotherapy, which aims to inhibit the proliferation of tumor cells and induce cancer cell death, is an applicable treatment for many cancers [5]. However, chemotherapy produces various important side effects and can frequently be followed by a multidrug resistance (MDR). The critical point is the access to chemotherapy that remains limited for most African populations due in particular to the availability and accessibility of molecules [6-8]. Faced with these difficulties, many studies have focused on the search for natural bioactive compounds, or even molecules, from plants used in traditional medicine. As an example, the first anti-cancer agents developed from plants were vinblastine (PubChem: 13342) and vincristine (PubChem: 5978). Both compounds are dimeric alkaloids isolated from the Madagascar periwinkle (*Catharanthus roseus*), which have significant cytotoxic activity and are used as antineoplastic agents in antitumor therapy [9]. During cell proliferation, they act by inhibiting the metaphase of the cell cycle and binding to microtubules that block mitotic spindle development. In tumor cells, these agents inhibit DNA repair and RNA synthesis machinery [10]. Indeed, plants are reservoirs of new chemical entities, providing a promising avenue for cancer research, in particular based on ethnobotanical data and traditional medical practices. The use of plant-based bioactive compounds to treat cancer is therefore a developing field. Plants in anti-cancer drug discovery would provide access to products that can be obtained more easily, quickly and cheaply, and thus accessible to the greatest number. While the

extraction of these compounds is usually environmentally friendly, their overall toxicity needs to be carefully considered. Most are selective, targeting tumor cells while sparing healthy cells [11]. Many phytochemical compounds and their analogues derived from African medicinal plants have been identified and are potential candidates of choice for the treatment of certain cancers, most of them are selective, targeting tumor cells while sparing healthy cells [11]. However, the number of clinical trials with natural bioactive compounds is still limited (**Table 1**).

The aim of this review is to identify molecules derived from African plants that can be used in cancer chemotherapy, while describing the associated molecular mechanisms.

Current chemotherapy context (side effects, resistance and costs)

Antitumor therapies depend on the type and stage of the disease. As noted above, current options are surgery, radiation therapy and/or drug treatments [5]. The latter is based on chemotherapy, immunotherapy and targeted therapy [12].

Organs targeted by side effects

Long term treatments with chemotherapy agents entail severe damage or failure of multiple organs: kidneys [13], liver [14, 15], heart [16], blood [17], skin [18], nervous system [19], digestive system [20] and reproductive system [21, 22].

At the heart level, chemotherapies can lead to hypertrophies, arrhythmias, and/or heart attacks [23]. Doxorubicin, daunorubicin, epirubicin and idarubicin, members of the anthracycline class, have often been reported as cardiotoxic [24]. Indeed, the quinone group of anthracyclines acts on DNA and causes single and double strand breaks, and also generates reactive oxygen species (ROS) toxic to the heart [25]. Cyclophosphamide, ifosfamide, cisplatin, 5-fluorouracil, paclitaxel and docetaxel may also be cardiotoxic [16].

Kidneys, being involved in the elimination of many substances such as urea, uric acid, creatinine and xenobiotics [13], any nephrotoxic compound can alter their plasma concentra-

Anti-cancer molecules from African medicinal plants

Table 1. Molecules isolated from African medicinal plants in clinical trials as anti-cancer drugs

Compounds	Phase of clinical trials	Type of cancer/dose/way of administration/mechanism of action	Publications of results ClinicalTrials.gov ID
Resveratrol	Phase I	Colon cancer/20 mg daily/oral/modulate patient Wnt signaling pathway	[118] NCT00256334
Lycopene	Phase II	Metastatic prostate cancer/30 mg daily/oral/chemotherapy	[156] NCT00068731
Quercetin	Phase I	Oral mucus/250 mg quercetin capsules daily for 3 weeks/oral/Chemotherapy	NCT01732393
Isoquercetin	Phase II/III	Pancreatic, lung or colorectal cancers/1000 mg daily for 28 days/oral/prevent venous thromboembolic events in cancer patients	[157] NCT02439385
Artesunate (Semi-synthetic derivative of artemisinin)	Phase I	Metastatic breast cancer/200 mg daily/oral/chemotherapy	[158] NCT00764036
Curcumin	Phase III	Prostate cancer/1000 mg daily/oral/chemotherapy	NCT03769766
Epigallocatechin gallate	Phase I	Colon or rectum cancer/450 mg twice daily/orally/Evaluate chemopreventive effect in patients	NCT02891538

tions [26]. Several anti-cancer drugs have strong nephrotoxicity, including cisplatin, ifosfamide, mitomycin, methotrexate and gemcitabine [27]. They act directly on nucleic acids causing not only a blockage of DNA and RNA synthesis, but also DNA damages. All these alterations can then lead to decreased creatine clearance, impaired magnesium reabsorption, decreased glomerular filtration rate, acute kidney injury, distal renal tubular acidosis, microangiopathy, chronic renal failure [28, 29].

Chemotherapy-induced gastrointestinal toxicity most often causes intense pain, nausea, infections and/or diarrhea [20, 30]. Several anti-cancer drugs are responsible for this toxicity, including cisplatin, doxorubicin, cyclophosphamide, methotrexate, bleomycin, 5-fluorouracil, irinotecan, fluorouracil, and capecitabine [27]. The imbalance of the intestinal microbiota (dysbiosis) can also weaken the immune system and reduce the quality of life of patients [20].

The liver is involved in numerous homeostasis including detoxification, drug metabolism and waste excretion [31]. Irinotecan, cisplatin, oxaliplatin, erlotinib, gefitinib, imatinib, azathioprine, 6-mercaptopurine, and 6-thioguanine, cytarabine, and dacarbazine are often associated with high hepatotoxicity [14, 15]. Hepatitis, cholestasis, steatosis, veno-occlusive disease, sinusoidal obstruction syndrome and fibrosis are among the most common hepatotoxic side effects of chemotherapy [32, 33]. As with other organs, DNA alterations are often the *primum movens* of these conditions.

The chemotherapeutic molecules, more precisely those of the class of alkylating agents, affect the normal functioning of the gonads, especially in the production of gametes. In men, they not only cause damage to spermatocytes but also act on spermatogonia stem cells, resulting in the inability of cells to repopulate seminiferous tubules after stopping treatment [21, 34]. In women, alkylating agents and anthracyclines cause a reduction in the pool of primordial follicles, premature ovarian failure, and oocyte loss [22].

Central or peripheral nervous systems are also secondary targets for some chemotherapy. Peripheral neuropathy can be manifested by paresthesia of the hands and feet, a decrease in deep tendon reflexes, paraparesis or mandibular pain. These clinical manifestations are generally due to the use of platinum-based drugs, particularly cisplatin [35]. Central nerve toxicity is mainly induced by cyclophosphamide, ifosfamide, melphalan, busulfan, aracytin, cytarabine and methotrexate. These drugs, particularly methotrexate and cytarabine, cause leukoencephalopathy and cerebellar dysfunction, leading to cognitive impairment, often transient dementia, and focal deficits [36].

Chemotherapy administration is often associated with skin manifestations that can be grouped into three major groups: alopecia, hand-foot syndrome, and allergic reactions [37]. Alopecia, which refers to hair loss, is caused by anthracyclines, cyclophosphamides, doxorubicin, cisplatin and vinorelbine. These

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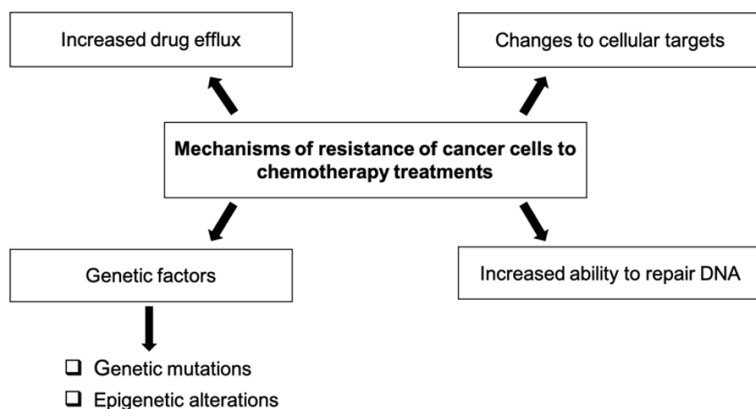


Figure 1. Summary of the main mechanisms of resistance of cancer cells to chemotherapy.

molecules act on the cells of the hair bulb in the renewal phase, causing fragility and hair loss. All chemotherapy products have the potential to cause allergic reactions (rash, erythema, allergic shock) that are manifested by swelling of the face, lips and/or tongue, shortness of breath, fever or severe skin reactions (itching, redness, pimples) [18].

Finally, it is the hematological sphere that is most affected by chemotherapy-induced toxicity since it can affect red blood cells, leukocytes and/or platelets, causing anemia, leukopenia and/or thrombocytopenia [38]. Anemia is prevalent in 30-90% of cancer patients. As red blood cells are involved in the transport of oxygen to various organs of the body, their reduction results primarily in intense fatigue, difficulty breathing, paleness and high blood pressure [17]. The anti-cancer involved are essentially methotrexate and doxorubicin. Leukopenia follows a precipitous decrease in white blood cells caused by alkylating agents, anthracyclines and topoisomerase inhibitors. This decrease in leukocytes reduces the body's ability to resist infection [39]. Thrombocytopenia, which is responsible for bleeding-related clotting disorders, is more common with mitomycin-C and gemcitabine [40].

Resistance mechanisms

Resistance to cancer treatments is very common. It is responsible for about 90% of cancer patient deaths [41]. This drug resistance of cancer cells is linked to several molecular mechanisms, the main ones being: an abnor-

mal increase in drug efflux; the occurrence of genetic mutations and/or epigenetic alterations; modification/adaptation of molecular targets; increased ability to repair DNA [42] (Figure 1).

The efflux mechanism of cancer drugs in cancer cells results in a significant reduction in the therapeutic effect of the administered drugs. This resistance is established by a large accumulation of membrane proteins promoting the export of xenobiotics belong-

ing to the superfamily of carrier's ABCs (ATP-binding cassettes). This multigene family includes ABCA3, ABCB 1 (also known as MDR 1 or P-glycoprotein P-gp), ABCC 1 (MRP 1), ABCC 3 (MRP 3/cMOAT-2), ABCG 2 (ABCP/MXR/BCRP) [2]. The ABCB1-encoded P-glycoprotein is involved in the efflux of doxorubicin, daunorubicin, vincristine, etoposide, colchicine, camptothecin and methotrexate. ABCB1 being overexpressed in cancer cells, cells become chemoresistant. Multidrug-resistant proteins (MRP) are also involved in the efflux of several anti-cancer drugs such as methotrexate (MRP 1, MRP 2 and MRP 4), etoposide (MRP 3, MRP 6), 6-mercaptopurine (MRP 5), 6-thioguanine (MRP 5) and 5-fluorouracil (MRP 8) [43]. Aung *et al.* (2017) found that resistance genes (ABCA4 and ABCA12) were overexpressed in MCF-7 human breast cancer cells after docetaxel treatment. However, a decrease in their expression is observed when curcumin (phytochemical compound) is associated with docetaxel [44].

Failure of chemotherapy may also be caused by genetic mutations already present or acquired during tumor progression. The most frequently mutated gene encodes the tumor suppressor TP53, qualified as guardian of genome stability. Mutations in the p53 gene most often result in the loss of protein function and changes in the pro-apoptotic balance leading to drug resistance. The correlation between mutation status p53 and cytotoxic drug susceptibility was demonstrated in a study conducted by the National Cancer Institute, which examined 60 cell lines and over 100 cancer drugs [45, 46].

Overexpression of p53 mutant with reduced or repealed function is often associated with resistance to the agents tested in the study (cisplatin, temozolomide, doxorubicin, gemcitabine, cetuximab) [47]. In addition, changes in molecular targets and signaling pathways modify the sensitivity of tumor cells to cancer drugs. For example, the mechanism of action of anthracyclines is based on their ability to interact with topoisomerase DNA. Mutations in the TOP1 gene, encoding topoisomerase 1, lead to a decrease in the ability of anthracyclines to interact with their targets [46]. Epigenetic changes, such as DNA methylation (hypermethylation of tumor suppressor genes and hypomethylation of oncogenes), histone modification (methylation, acetylation, phosphorylation, etc.) and alterations in the expression of specific miRNAs are also responsible for resistance to cancer drugs [48]. Another molecular mechanism leading to chemoresistance is the ability of cells to repair damage caused by molecules through DNA repair mechanisms. One of the main pathways is the nucleotide excision (NER) repair pathway involving the endonuclease XPF-ERCC1 [49]. The NER pathway involves several steps: recognition of DNA damage, DNA unfoldment, damage cleavage, polymerization, and ligation [50]. Cancer cells have a higher level of XPF and ERCC1, leading to treatment failure [51].

Costs

Beyond the side effects and the development of resistance to treatments, the main difficulty in Africa is the availability and accessibility to essential cancer medicines, new cancer medicines, and supportive treatment. Besides, the participation of African populations in clinical trials remain low-access. Indeed, in some sub-Saharan countries, cancer treatment is not covered by national health-care system, which forces patients to bear the cost of screening and treatment [52]. Relative to chemotherapy treatment, the cost varies depending on the type of cancer, the molecules used, the chemotherapy protocol and the rhythm. On average, the price varies between \$170 and \$6,700 every three weeks, for 6 sessions, with the possibility of further treatment. This cost is out of reach for most patients, resulting in increased cancer mortality [8]. These difficulties have led to a real decline in the development of new syn-

thetic and seminal drugs. In addition, this has led to the revival of herbal therapies in the form of dietary supplements and preparations of botanical origin. The preventive or therapeutic potential of several phytochemical compounds has been evaluated pharmacologically for several decades [53].

Inventory and anti-cancer molecules of African medicinal plants

Methods

The study protocols: This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [54].

Selection criteria: Articles were selected by reviewing the relevant titles and abstracts in each electronic database. Full-text articles were reviewed, duplicate and out-of-scope studies were excluded. The inclusion criteria for this review were: I. Full-text articles on molecules isolated from African medicinal plants, and their anti-cancer activities and mechanisms of action; II. Articles published over the past 17 years (2005-2022); III. Written in English.

Systematic research strategy: The systematic search ran from October to November 2022, using three well-known search engines: ScienceDirect, Google Scholar and PubMed. The keywords used in the three search engines were: (“bioactive compounds of African medicinal plants” OR “phytochemicals from African medicinal plants” OR “anti-cancer molecules of African medicinal plants”) AND (“cancer” OR “carcinoma” OR “tumor”), using the appropriate Boolean operators for each database. Research conducted on the ScienceDirect search engine identified 4,752 items containing 1,839 research articles and 1,404 journal articles. Google Scholar gave 3210 journal and research articles. A similar PubMed search yielded a total of 322 results (**Figure 2**).

Results

Although Africa has an exceptional plant biodiversity, very few studies have been conducted on the anti-cancer properties and molecular mechanisms of action of bioactive molecules isolated from endemic medicinal plants. In view

Anti-cancer molecules from African medicinal plants

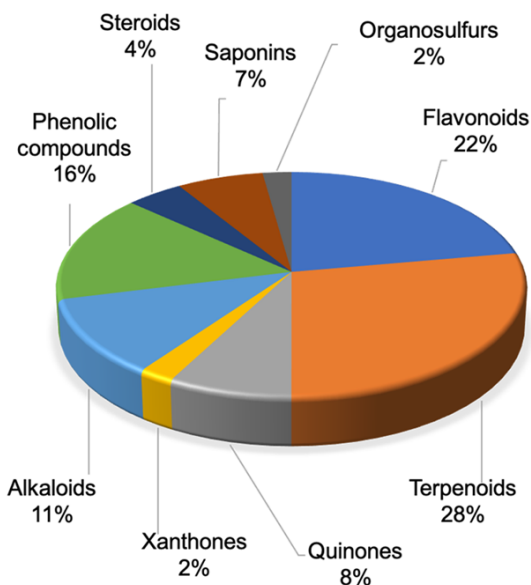
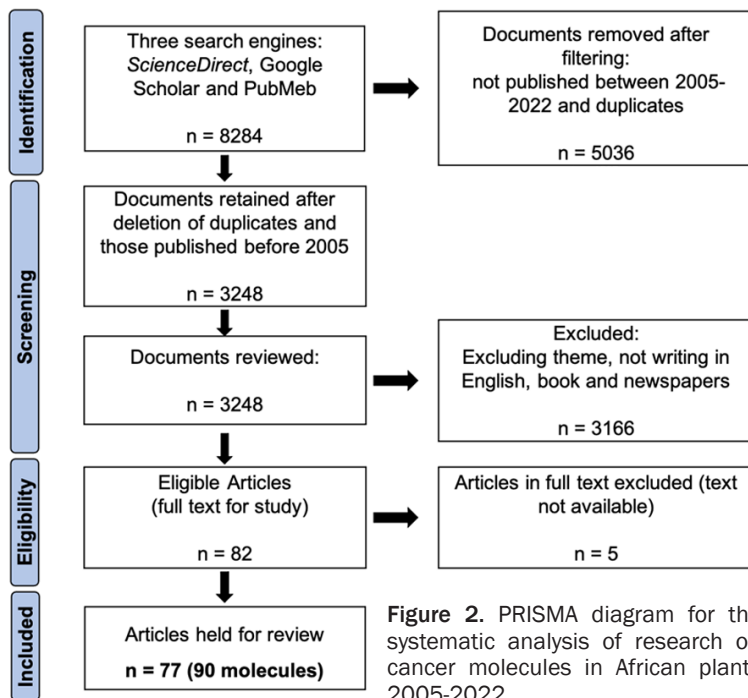


Figure 3. Phytochemical groups of bioactive molecules.

of the increasing incidence of various cancers and the difficulty of access to synthetic molecules, significant efforts have been made in recent years to develop these studies. Our research identified 77 articles that met the inclusion criteria and were therefore collected for this review (**Figure 2**). A total of 90 compounds from eight chemical groups were

identified for this study: alkaloids, flavonoids, polyphenols, quinones, saponins, steroids, terpenoids, and xanthoness. Our data show that 28% of the molecules are terpenoids, followed by flavonoids (22%), phenolic compounds (16%), alkaloids (11%), quinones (8%) and saponins (7%). Steroids, xanthoness and organosulfur are the least represented (with 4%, 2% and 2% respectively) (**Figure 3**). The compounds in our study are derived from medicinal plants from 15 African countries including Algeria, Botswana, Burkina Faso, Cameroon, Congo, Ivory Coast, Egypt, Ghana, Kenya, Morocco, Mozambique, Nigeria, South Africa, Tunisia and Uganda. In this way, Cameroon, Morocco and

Nigeria are the countries with the most compounds with 33, 16 and 12 compounds, respectively (**Figure 4A**). The number of anti-cancer compounds isolated from African plants was grouped according to the geographical area where the plants were collected. Most compounds were isolated from plants harvested in Central Africa (35), followed by North Africa (23), West Africa (17), South Africa (8) and finally East Africa (7) (**Figure 4B**). Indeed, the predominance of bioactive molecules from Central African plants may be due to the fact that this tropical region of Africa has the greatest diversity of plant species. Also, the Mediterranean climate zone with winter precipitation in North Africa has a great diversity of species, which could explain the proportion obtained in North Africa [55].

Mechanisms of action of anti-cancer molecules in African medicinal plants

The listed molecules, their PubChem accessibility number available, the cells tested, their activity and the country of collection are shown in **Table 2**.

In the following chapters, the numbers refer to the molecules listed in the table. The main sites of action of bioactives molecules from African medicinal plants at the level of apoptotic path-

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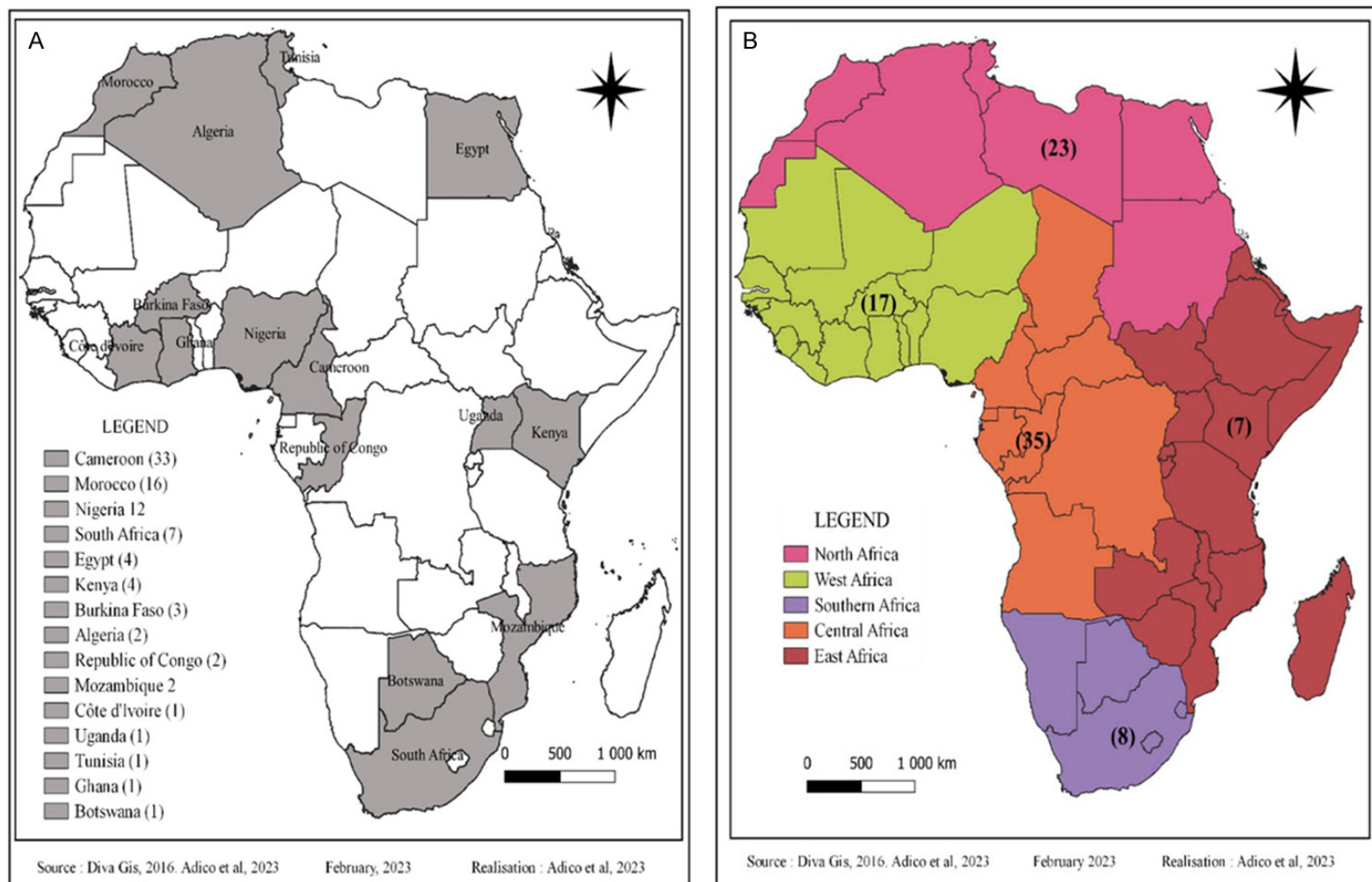


Figure 4. Number of anti-cancer molecules isolated from African medicinal plants. A. By country; B. By region.

Anti-cancer molecules from African medicinal plants

Table 2. Lists of molecules identified by bibliographic research

Molecules	Plants	Cell lines used	Activities	Country	References
Flavonoids					
2',4'-dihydroxy-6'-methoxychalcone (1) (PubChem: 67218246)	<i>Erythrina abyssinica</i>	MCF-7	IC50: 6.30 µM	Kenya	[56]
4'-hydroxy-2',6'-dimethoxychalcone (2) (PubChem: 71597852)	<i>Polygonum limbatum</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-})	IC50 < 10 µM	Cameroon	[61]
Luteolin (3) (PubChem: 5280445)	<i>Cyperus rotundus</i>	HepG2	IC50: 10.02 µM	Egypt	[57]
Isonorautenol (4) (PubChem: 73649)	<i>Erythrina senegalensis</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 < 22 M against all cell lines	Cameroon	[159]
Quercetin (5) (PubChem: 25130254)	<i>Gaillardia aristata</i>	MCF7 and HCT116	IC50: 2.2 and 1.7 µg/mL	Egypt	[70]
Gancaonin Q (6) (PubChem: 480802)	Genus <i>Dorstenia</i>	CCRF-CEM, CEM/ADR5000, PF-382, HL-60, MCF-7, MiaPaCa-2, SW-680, 786-O, U87MG, A549, Colo-38, HeLa, CaSki, Capan-1	IC50 < 20 µg/ml	Cameroon	[65]
6,8-diprenyleriodictyol (7) (PubChem: 4063836)					
4-hydroxy lonchocarpin (8) (PubChem: 5889042)					
Rutin (9) (PubChem: 5280805)	<i>Buddleja asiatica</i>	HepG2	IC50: 0.84 µM	Egypt	[69]
Dorsmanin F (10) (PubChem: 10527064)	<i>Dorstenia mannii</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 between 5.34 and 33.30 µM	Cameroon	[63]
Poinsettifolin B (11) (PubChem: 11798732)	<i>Dorstenia poinsettifolia</i>		IC50 between 1.94 and 28.92 µM		
Apigenin (12) (PubChem: 5280443)	<i>Gaillardia aristata</i>	HCT116 and MCF7	IC50: 1.4 and 1.8 µg/MI	Egypt	[70]
Kaempferol-3-methoxy-7-O-α-L-rhamnoside (13) (PubChem: 5280863)			IC50: 2.55 and 5.4 µg/ml		
Alpinumisoflavone (14) (PubChem: 5490139)	<i>Ficus chlamydocarpa</i>	CCRF-CEM, CEM/ADR5000	IC50: 9.60 and 5.91 µM	Cameroon	[64]
Abyssinone IV (15) (PubChem: 4063835)	<i>Erythrina sigmoidea</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2, AML12	IC50 < 30 µM	Cameroon	[62]
Sigmoidin I (16) (PubChem: 101667574)					
6α-hydroxyphaseollidin (17) (PubChem: 44257482)					
Sophorapterocarpan A (18) (PubChem: 14017299)					

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Isobavachalcone (19) (PubChem: 5281255)	<i>Dorstenia barteri</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-BCRP	IC50: 2.90; 3.73 and 2.93 μ M	Cameroon	[160]
Terpenoids					
2'-Hydroxy-4,4',5'-6'-tetramethoxychalcone (20) (PubChem: 6253276)	<i>Chromolaena odorata</i>	Cal51, MCF7, MDA-MB-231 and HeLa	IC50: 20 mM	Ivory Coast	[72]
Betulin (21) (PubChem: 72326)	<i>Parinari curatellifolia</i>	HeLa	IC50: 1.503/ml	Nigeria	[86]
Loliolide (22) (PubChem: 100332)	<i>Heliotropium bacciferum</i>	HCT116 and DLD1	IC50 between 0.236 and 0.395 mM	Algeria	[73]
Isololiolide (23) (PubChem: 11019783)					
Lupeol (24) (PubChem: 259846)	<i>Alstonia boonei</i>	CACO2	GI50: 50 μ g/ml	Nigeria	[77]
Tomentosine (25) (PubChem: 6438142)	<i>Inula viscosa</i>	SiHa and HeLa	IC50: 7.10 and 5.87 μ M	Morocco	[74]
Artemisinin (26) (PubChem: 68827)	<i>Artemisia annua</i>	P815 and BSR	IC50: 12 et 52 μ M	Morocco	[161]
Galanal A (27) (PubChem: 3050416)	<i>Aframomum arundinaceum</i>	CCRF-CEM, MDA-MB-231-BCRP	IC50: 17.32 and 27.99 μ g/mL	Cameroon	[60]
Galanal B (28) (PubChem: 3086504)		CCRF-CEM, MDA-MB-231-BCRP	IC50: 19.81 μ g/mL		
Carvacrol (29) (PubChem: 10364)	<i>Thymus broussonetii</i>	P-815, K-562, CEM, MCF-7 and MCF-7/gem	IC50 between 0.042 and 0.125 μ M	Morocco	[79]
Thymol (30) (PubChem: 6989)			IC50 between 0.15 and 0.48 μ M		
Carveol (31) (PubChem: 7438)			IC50 between 0.11 and 0.45 μ M		
Carvone (32) (PubChem: 7439)			IC50 between 0.11 and 0.91 μ M		
Isoeugenol (33) (PubChem: 170833)			IC50 between 0.09 and 0.25 μ M		
Eugenol (34) (PubChem: 3314)			IC50 between 0.09 and 0.87 μ M		
Lycopene (35) (PubChem: 446925)	<i>Carica papaya</i>	HepG2	IC50: 22.8 μ g/ml	Uganda	[81]
Curcusone A (36) (PubChem: 175941)	<i>Jatropha curcas</i>	HeLa	IC50 between 0.11 and 0.45 μ M	Nigeria	[83]
Curcusone B (37) (PubChem: 175944)					
Curcusone C (38) (PubChem: 175942)					
Curcusone D (39) (PubChem: 175945)					

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Betulinic acid (40) (PubChem: 64971)	<i>Parinari curatellifolia</i>	HeLa	IC50: 1.503 µg/ml	Nigeria	[86]
Ursolic acid (41) (PubChem: 64945)	<i>Rosmarinus officinal</i>	HepG2, Hep3B, Huh7 and HA22T	IC50 = 25 µM	Morocco	[90]
Friedelin (42) (PubChem: 91472)	<i>Ficus drupacea</i>	HeLa, MCF-7, Jurkat, HT-29, and T24	Inhibition of proliferation of all lines. IC50 between 12.81 and 37.21 µM	South Africa	[88]
Oleanolic acid (43) (PubChem: 10494)					
Kaurenoic acid (44) (PubChem: 73062)	<i>Annona senegalensis</i>	293T, HeLa and PANC-1	IC50: 0.93; 0.74; 0.52 M	Nigeria	[92]
beta-amyrin (45) (PubChem: 225687)	<i>Prunus africana</i>	HEK293, HepG2 and Caco-2	IC50: 156; 206 and 81 mg/mL	Kenya	[91]
Quinones					
Damnacanthal (46) (PubChem: 2948)	<i>Garcinia huillensis</i>	PANC-1 and PSN-1	PC50 = 4.46 et 3.77 mM	Congo	[96]
Nordamacanthal (47) (PubChem: 160712)		PANC-1	PC50 = 62.5 mM	Congo	
2-acetylfuro-1,4-napthoquinone (48) (PubChem: 10331844)	<i>Newbouldia laevis</i>	MCF-7, HeLa, Caski, PF-382 and colo-38	IC50: 0.57 µg/ml	Cameroon	[95]
Thymoquinone (49) (PubChem: 10281)	<i>Nigella sativa</i>	A-549 and DLD-1	IC50: 13 and 5.9 µg/mL	Tunisia	[94]
Isosofuranonapthoquinone (50) (PubChem: -)	<i>Bulbine frutescens</i>	Jurkat T	At 25 µg/ml, 47% cell viability	Botswana	[98]
Plumbagin (51) (PubChem: 10205)	<i>Plumbago zeylanica</i>	A549, SPC212, DLD-1, Caco-2, MCF-7, HepG2, CRL2120	IC50 between 0.06 and 1.14 µM	Kenya	[97]
Rapanone (52) (PubChem: 100659)	<i>Rapanea melanphloes</i>	SPC212	IC50 = 2.27 µM		
Xanthones					
Cudraxanthone I (53) (PubChem: 86276176)	<i>Milicia excelsa</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2,	Inhibition of proliferation of all lines. IC50 between 2.78 M and 22.49 M	Cameroon	[100]
Xanthone V ₁ (54) (PubChem: 139068057)	<i>Vismia laurentii</i>	MCF-7, HeLa, Caski, PF-382 et colo-38	IC50: 0.56 µg/ml	Cameroon	[95]
Alkaloids					
Fagaridine chloride (55) (ChemSpider: 8889516)	<i>Fagara tessmannii</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2,	IC50 between 1.69 µM and 22.06 µM	Cameroon	[102]
Nitidine chloride (56) (ChemSpider: 23901)					

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Solamargine (57) (PubChem: 73611)	<i>Solanum aculeastrum</i>	SH-SY5Y	IC50: 15.62 µg/mL	South Africa	[162]
Tomatidine (58) (PubChem: 65576)		HeLa	IC50: 141.7 µM		[104]
Solasodine (59) (PubChem: 442985)		HeLa	IC50: 252.5 µM		
15-Hydroxyangustilobine A (60) (PubChem: 70698298)	<i>Alstonia boonei</i>	MCF-7	IC50: 26 µM	Ghana	[105]
Berberine (61) (PubChem: 2353)	<i>Berberis vulgaris</i>	MCF-7	IC50: 8.75 µM	Morocco	[163]
Tabernaemontanine B (62) (ChemSpider: 10222219)	<i>Tabernaemontana elegans</i>	HCT116	IC50: 0.5 µM	Mozambique	[106]
Tabernaemontanine C (63) (ChemSpider: 10202338)			IC50: 20 µM		
Arborinine (64) (PubChem: 5281832)	<i>Uapaca togoensis</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	Inhibition of proliferation of all lines. IC50 < 32 µM	Cameroon	[101]
Phenolic compounds					
Epigallocatechin gallate (65) (PubChem: -)	<i>Garcinia ovalifolia</i>	HL-60 and PC-3	IC50: 7 µg/mL	Cameroon	[107]
Isogallocatechin gallate (66) (PubChem: 11135781)			IC50: 4 and 8 µg/mL		
Resveratrol (67) (PubChem: 445154)	<i>Commiphora africana</i>	MCF7, A549, PC-3, HepG	IC50: 16.80; 21.74; 17.89 et 17.44 µM	Nigeria	[164]
Epigallocatechin gallate (68) (PubChem: 65064)	<i>Camellia sinensis</i>	NIH-pATMras	20 µM inhibited cell growth	Morocco	[90]
Isoxanthochymol (69) (PubChem: 10461245)	<i>Hypericum lanceolatum</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	Inhibition of cell line proliferation. IC50 between 0.83 µM and 14.70 µM	Cameroon	[108]
Guttiferone E (70) (PubChem: 5352088)					
Gallic acid (71) (PubChem: 370)	<i>Anogeissus leiocarpus</i>	B16-F10	GI50: 50 µg/ml	Nigeria	[165]
Ellagic acid (72) (PubChem: 5281855)					
Pycnanthuligenene A (73) (PubChem: 46186375)	<i>Pycnanthus angolensis</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 5.84 to 65.32	Cameroon	[64]
6-shogaol (74) (PubChem: 5281794)	<i>Zingiber officinale</i>	A549, SKOV3, SKMEL2, HCT15	IC50: 17.43; 15.72; 20.94 and 30.05 µg/ml	Morocco	[90]
6-gingerol (75) (PubChem: 442793)		A549, SKOV3, SKMEL2, HCT15	IC50: 9.58; 18.85; 12.12 and 12.57 µg/ml		

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Curcumin (76) (PubChem: 969516)	<i>Curcuma longa</i>	CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 between 6.25 and 19.69 µg/ml	Cameroon	[166]
Hypoxoside (77) (PubChem: 13785311)	<i>Hypoxis colchicifolia</i>	INS-1	IC50: 25 µM	South Africa	[167]
Hyperoside (78) (PubChem: 5281643)		MIA PaCa-2	IC50: 50 µM		
Steroids					
2"-Oxovoruscharin (79) (PubChem: 11410873)	<i>Calotropis procera</i>	A549, Hs683, U373, HCT-15 and LoVo	IC50: 2.7 nM	Burkina Faso	[122]
β-sitosterol (80) (PubChem: 222284)	<i>Parinari curatellifolia</i>	HeLa	IC50: 1.503/ml	Nigeria	[86]
UNBS-1450 (81) (PubChem: 11261970)	<i>Calotropis procera</i>	NSCLC	IC50: 10 nM	Egypt	[126]
Diosgenin (82) (PubChem: 99474)	<i>Trigonella foenumgraecum</i>	1547	IC50: 40 µM (24 h)	Morocco	[86, 127]
Saponins					
Balanitin 6 (83) (PubChem: 44576182)	<i>Balanite aegyptiaca</i>	NSCLC and U373	IC50: 0.3 and 0.5 µM	Burkina Faso	[132]
Balanitin 7 (84) (PubChem: 10953190)					
Olean-12-en-3-β-O-D-glucopyranoside (85) (PubChem: -)	<i>Tetrapleura tetraptera</i>	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	Inhibition of proliferation of all lines. IC50 between 10.27 µg/mL and 23.61 µg/mL	Cameroon	[128]
Daucosterol (86) (PubChem: 5742590)	<i>Crateva adansonii</i>	PC-3 and DU145	CC50: 17.45 and 29.25 µg/mL	Cameroon	[131]
Ardisiacrispin B (87) (PubChem: 10441164)	<i>Ardisia kivuensis</i> Taton	CCRF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 between 1.20 and 6.76 µM	Cameroon	[129]
Progenin III (88) (PubChem: 146157809)	<i>Raphia vinifera</i>	CCF-CEM, CEM/ADR5000, MDA-MB-231-pcDNA, MDA-MB-231-BCRP, HCT116 (p53 ^{+/+}), HCT116 (p53 ^{-/-}), U87MG, HepG2	IC50 between 1.59 and 31.61 µM	Cameroon	[130]
Organosulfur					
Allicin (89) (PubChem: 65036)	<i>Allium sativum</i>	HepG2	IC50: 35 µM	Morocco	[90, 133]
S-allylcysteine (90) (PubChem: 9793905)	<i>Allium sativum</i>	A2780	IC50 < 6.25 mmol/l (96 h)		[90, 134]

IC50: median concentration for inhibition of cell survival of 50%; CC50: concentration necessary to obtain 50% of the cytotoxic effect; GI50: concentration necessary for inhibition of cell growth of 50%; PC50: preferential cytotoxicity to obtain 50% of the effect studied. Since cell survival was the parameter measured for each molecule, we can consider these values to be comparable.

ways and different phases of the cell cycle in cancer cells presented in this review are summarized in **Figure 5A** and **5B**.

Flavonoids

Flavonoids are metabolites with polyphenolic structure widely distributed in plants, carrying anti-cancer biological properties. Plants with anti-cancer activity in Africa present flavonoids in the second highest percentage within their entire range of compounds. As examples, 2',4'-dihydroxy-6'-methoxychalcone (1), isolated by Kuete *et al.* from *Erythrina abyssinica* collected in Kenya, induces apoptosis of MCF-7 by activating caspases 3/7 and 9, and decreasing mitochondrial membrane potential which increases the production of reactive oxygen species (ROS) [56]. Luteolin (3), isolated from *Cyperus rotundus* collected in Egypt, shows significant cytotoxicity against cancer cells HepG2 compared to the reference drug doxorubicin [57]. This compound activates the extrinsic and intrinsic apoptotic pathways (**Figure 5A**), particularly by increasing the expression of the DR5 receptor in cervical or prostate cancer cells [58]. It activates the intrinsic pathway by inducing DNA damage and activating p53, thus increasing the level of caspases 9 and 3, and the Bcl-2 cleavage in cancer cells. Luteolin can also block the cell cycle in G1 phase [59]. Cameroonian compounds (2), (4), (10), (11), (14), (15), (16), (17), (18) and (19) isolated from *Polygonum limbatum* (2), *Erythrina senegalensis* (4), *Dorstenia mannii* (10), *D. poinsettifolia* (11), *Ficus chlamydocarpa* (14), *Erythrina stemoidea* (15; 16; 17 and 18) and *Dorstenia barteri* (19) induce apoptosis of CCRF-CEM leukemia cells mediated by the disruption of mitochondrial membrane potential (MMP) and increased ROS production *via* the activation of initiator caspases 8 and 9, and effector caspase 3/7 [60-64]. Compound (2) arrests the cell cycle between G0/G1 phase [61]. An anti-angiogenic activity of compounds (6), (7) and (8) isolated from genus *Dorstenia* (Cameroon), followed by activation of caspase 3/7 induce apoptosis [65]. These molecules could become the basis of new cytotoxic drugs against resistant multifactorial cancers. The anti-cancer effects of quercetin (5) appear to be mediated by stopping the cell cycle in G2/M phases. It also promotes the expression of the Bax, p53, caspase-3 and cytochrome-c genes involved in cell death, while decreasing the expression of

AKT and Bcl-2 [66]. Rutin (9) inhibits proliferation by modifying the BAX/Bcl ratio in human glioma CHME cells, to activate the intrinsic apoptotic pathway [67]. It regulates upward the expression of the p53 cancer gene [68]. This compound (9) isolated from *Buddleja asiatica* leaves (Egypt) has a significant cytotoxic activity against a HepG2 cell line [69]. Compounds (5), (12) and (13), isolated from the Egyptian plant *Gaillardia aristata*, show cytotoxicity against HCT116 and MCF-7 colon and breast cancer cell lines, respectively [70]. The mechanism of action of apigenin (12) in cancer cells consists mainly in blocking phosphorylation of the JAK2 and STAT3 pathways. Rahmani *et al.* demonstrated a cytotoxic effect on MDA-MB-453 breast cancer cells by inhibiting the STAT3 signaling pathway through increased caspases 3 and 8 expression levels [71].

Terpenoids

Compound (20) isolated from *Chromolaena odoratae* harvested in Ivory Coast, displays cytotoxic and anticlonogenic effects on several cell lines (Cal51, MCF7 and MDAMB-468). The association of this molecule with the Bcl2 inhibitor ABT737 significantly improves apoptosis in Cal51 breast cancer-derived cells [72]. Loliolide (22) and isololiolide (23) isolated from *Heliotropium bacciferum* (Algeria) induce cytotoxicity in cancer cell lines HCT116 and DLD1 [73]. Tomentosine (25) isolated from *Inula viscosa* (Morocco) and galanal A (27) and B (28) isolated from *Aframomum arundinaceum* (Cameroon) induce apoptosis in cancer cells by generating ROS and promoting cytochrome c release, and increasing Caspase-3. Galanal A (27) and B (28) also reduce Bcl-2 expression, leading to the activation of the intrinsic apoptotic pathway. In addition to inhibiting telomerase expression, the compound (25) stops the cell cycle in G2/M phase [60, 74]. The anti-cancer effects of artemisinin (26) isolated from *Artemisia annua* (Morocco) appear to be mediated by tumor cell cycle arrest by modulating the levels of cyclins and CDK proteins. Thus, the compound triggers G1 phase cell cycle arrest of prostate cancer cells, accompanied by down regulation of CDK2 and CDK4 proteins [75]. Artemisinin (26) and its derivatives also inhibit both tumor cell invasion and metastatic processes of tumor cells by enhancing the matrix metalloproteinases (MMPs) expression and regulating the tumor microenvironment.

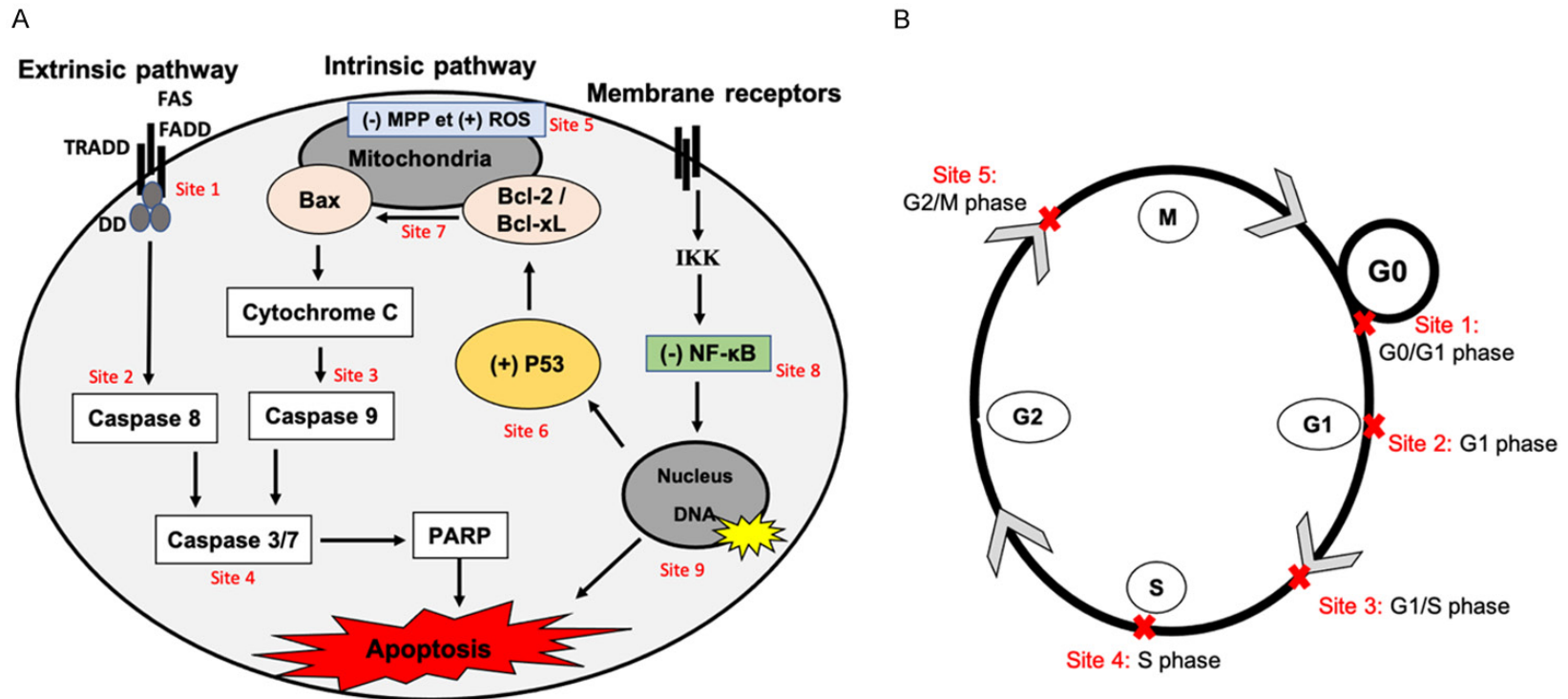


Figure 5. Sites of action of the bioactive molecules from African medicinal plants as anticancer agents. A. Therapeutic approaches of bioactive molecules from African medicinal plants targeting apoptosis pathways in cancer cells. Anticancer molecules from African medicinal plants are able to induce cancer cell apoptosis via: The apoptotic extrinsic pathways activation (site 1); activation of caspases 8, -9, -7 and -3 and PARP cleavage (site 2-3-4); apoptotic intrinsic pathways activation by loss of the potential of the mitochondrial membrane (MMP), ROS increase, Bcl2/Bcl-xl anti-apoptotic proteins inhibition, p53 activity and cytochrome c release, (site 5-6-7); inhibition of IKK/NF-κB activity (site 8) and preventing the transcription of anti-apoptotic regulators (site 9). B. Therapeutic approaches of bioactive molecules from African medicinal plants targeting cell cycle in cancer cells. Anticancer molecules from African medicinal plants act mainly on cell cycle to inhibit the proliferation of cancer cells at G0/G1 (site 1), G1 (site 2), G1/S (site 3), S (site 4) and G2/M (site 5).

MMP-2 and MMP-9 are strongly correlated with tumor cell invasion and metastasis [76]. Lupeol (24), isolated from *Alstonia boonei*, collected in Nigeria, is cytotoxic on CACO2 intestinal cells [77]. The mechanism of action involves a decreased expression of anti-apoptotic proteins Bcl-2 and Bcl-xL, and the induction of the apoptosis of MCF-7 cells [78]. Monoterpenes (29), (30), (31), (32), (33) and (34) isolated from *Thymus broussonetii* (Morocco) were characterized with anticancer properties [79]. Compounds (29) and (31) induce the cytotoxic effect by stopping the cell cycle in S phase, while compounds (30) and (33) arrest the cell cycle in G0/G1 phase. However, no effects on the cell cycle were observed for carvone (32) and eugenol (34) [80]. Lycopene (35) isolated from *Carica papaya* (Uganda) inhibits the viability of HepG2 cancer cells [81]. The cytotoxicity of compound (35) is also associated with an inhibition of the cell cycle progression. This occurs through the reduction of cyclin D and p27 levels, leading to cycle arrest in G1 phase of breast and endometrial cancer cells and increases phosphorylation of the anti-oncogenes p53 and Rb [82]. *Jatropha curcas*, collected in Nigeria, was used to isolate curcusones A (36), B (37), C (38) and D (39) which have cytotoxic activities against cervical HeLa cells [83]. Cytotoxicity of compound (37) is associated with cytochrome c release, activation of caspase-3 and caspase-9, deregulation Bcl-xL/Bax, and decreased survival, resulting in apoptosis [84]. Curcusine C (38) inhibits the metastatic process by reducing the expression of certain MMPs [85]. Betulinic acid (40) isolated from *Parinari curatellifolia* (Nigeria) [86], triggers cancer cell apoptosis by activating the mitochondrial pathway. In fact, Betulinic acid (40) significantly increases the level of production of reactive oxygen species (ROS) and modifies the mitochondrial membrane potential gradient, followed by the release of cytochrome c, resulting in apoptosis of caspase-dependent cancer cells. It also activates the transcription 3 (STAT3) signaling pathways of cancer cells and nuclear factor NF- κ B [87]. Friedelin (42) and oleanolic acid (43) isolated from *Ficus drupacea* (South Africa) are cytotoxic against several cell lines [88]. Friedelin (42) leads to cancer cell death not only through apoptosis but also by necrosis, increasing the expression of tumor suppressor genes Cdkn1a, pRb2, p53, Nrf2, caspase-3 and decreasing the expression of Bcl-2, mdm2 and PCNA [89]. Ursolic

acid (41), isolated from *Rosmarinus officinal* (Morocco), causes apoptosis through increased expression of Bax and caspases 3 and 8 [67, 90]. β -amyrin (45) isolated from *Prunus africana* (Kenya) induces apoptosis in Caco-2 cell lines [91]. Kaurenic acid (44) isolated from *Annona senegalensis* (Nigeria) possesses cytotoxicity and anticancer effect against HeLa and PANC-1 cell lines [92]. The apoptotic effect of β -amyrin (45) was attributed to the increase of Bax and reduction of Bcl-2 in Hep-G2 hepatic cells. It also causes the G2/M cycle arrest and activates p38 and JNK signaling channels [93].

Quinones

The quinones (46), (47), (48), (49), isolated from the plants *Garcinia huillensis* for (46) and (47) (Congo), *Newbouldia laevis* for (48) (Cameroon) and *Nigella sativa* for (49) (Tunisia), respectively, induce apoptosis through irreparable DNA damage and stopping the cell cycle in S phase. Compounds (46) and (47) trigger intrinsic apoptosis through activation of caspases-3/7 and 9, while thymoquinone (49) activates the extrinsic pathway through caspase 8 and 3 [94-96]. Increased ROS production results in decreased MMP in breast cancer cells (MCF-7) treated with plumbagin (51) isolated from *Plumbago zeylanica* (Kenya) or rapanone (52) from *Rapanea melanphloes* (Kenya) [97]. Isofuranonaphthoquinone (50) isolated from *Bulbine frutescens* (Botswana) is considered an excellent anti-cancer agent due to its actions similar to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) [98]. Mechanistic studies suggest that isofuranonaphthoquinone (50) can exert its activity by generating ROS that lead to cell death and inhibition of drug efflux pumps. The efficacy of compound (50) was highest on Jurkat lymphocyte cells when combined with BCNU. Therefore, this compound (50) is a potential candidate for the development of new anti-cancer drugs and a complementary compound in combination therapy regimens [99].

Xanthones

Exposure to cudraxanthone I (53) and xanthone V1 (54) from *Millicia excelsa* and *Vismia laurentii*, respectively from Cameroon, increases the expression of caspases 3/7 and blocks the S-phase cell cycle in CCRF-CEM cells. The compound (53) also activates caspases 8 and 9 [95, 100].

Alkaloids

Fagaridine chloride (55), nitidine chloride (56) extracted from *Fagara tessmannii* (Cameroon) and Arborinine (64) isolated from *Uapaca togoensis* (Cameroon) inhibit the proliferation of CCRF-CEM cells by activating caspases 3/7, 8 and 9 and increasing ROS production. Arborinine (64) also blocks the cell cycle in G0/G1 and S phases [101, 102]. These compounds require further studies for the development of new cytotoxic agents against resistant multifactorial cancers. Solamargine (57) isolated from *Solanum aculeastrum* (South Africa) is an alkaloid with non-selective cytotoxicity against the SH-SY5Y cancer cell lines and P-glycoprotein inhibition [103]. This compound (57) activates the expression of external death receptors, such as tumor necrosis factor receptor I (TNFR-I), FAS receptor, TNFR-I-associated death domain (TRADD) and FAS-associated death domain (FADD) and also increases the intrinsic ratio of Bax to Bcl-2 by increasing and decreasing Bcl-2 and Bcl-xL expressions. These effects cause the release of mitochondrial cytochrome c and the activation of caspases-8, -9 and -3 in breast cancer cells [103]. Tomatidine (58) and solasodine (59) isolated from *Solanum aculeastrum* (South Africa) inhibit HeLa cell growth by blocking the cell cycle at the G0/G1 phase [104]. Isolated from *Alstonia boonei* (Ghana), 15-hydroxyangustilobine A (60) induces cell cycle arrest at G2/M phase in MCF-7 breast cancer cells, at least partially triggering apoptosis [105]. The level of expression of caspase-3 was increased when HCT116 cells were treated by tabernaeanine B (62) and C (63) isolated from *Tabernaemontana elegans* (Mozambique). These compounds also cause cell shrinkage and condensation, cell nuclei fragmentation, plasma membrane detachment, and chromatin condensation [106], signs of apoptosis. Berberine (61), isolated from *Berberis vulgaris* collected in Morocco, inhibits the proliferation of MCF-7 cells by inducing cell apoptosis through the decrease of MMP and increase of ROS production [107].

Phenolic compounds

Compounds épigarcinol (65) and isogarcinol extracted from *Garcinia ovalifolia* (Cameroon) (66) inhibit HL-60 and PC-3 cell proliferation with an inhibition concentration (IC50) ranging

from 4 to 8 µg/mL, depending on the line. These compounds induce G2/S phase cell cycle arrest, MMP disruption, and ROS production in HL-60 cells [107]. Isoxanthochymol (69), guttiferone E (70) and pycnanthulignene A (73), isolated from *Hypericum lanceolatum* for compounds (69) and (70) *Pycnanthus angolensis* for compound (73) (Cameroon), degrade the mitochondrial membranes of CCRF-CEM cells. Compounds (69) and (70) cause apoptosis via the activation of caspases 3/7, 8 and 9 as well as the loss of MMP [64, 108]. For compound (76) isolated from *Curcuma longa* (Cameroon), the expression of migration-associated proteins, including matrix metalloproteinase (MMP)-9, NF-κB, and claudin-3, decreases while its concentration increases in colorectal cells (HCT116). Therefore, curcumin (76) promotes cell apoptosis and inhibits tumor cell metastasis by regulating the NF-κB signaling pathway [109]. *Zingiber officinale*, as common ginger, is a rhizomatous perennial plant used in Africa as a spice in food and beverages. It is also used as a remedy for several digestive disorders [110, 111]. As pointed out by Bayala et al. in a study conducted in Burkina Faso [112], the essential oil of this plant is known for its anti-inflammatory properties. Among the compounds isolated, 6-gingerol (75) and 6-shogaol (74) appear to be part of the molecules responsible for many biological effects especially anti-cancer activity [113]. In addition to stopping the cell cycle at the G2/M phase, the autophagy of MCF-7 and T47D lines derived from breast cancers is also inhibited by 6-gingerol (75) [114]. 6-gingerol (75) promotes apoptosis by increasing ROS production, activating the p53 protein and inhibiting the degradation of CDK-inhibiting proteins (p27 and p21) in LoVo colorectal cells [115], and activates caspases 3/7, 8 and 9 in the colorectal cells SW-480 [116]. Two compounds isolated from *Anogeissus leiocarpus* (Nigeria), gallic acid (71) and ellagic acid (72) decrease the proliferation of human pancreatic cell lines MIA PaCa-2 and PANC-1 by activating caspases 3, 9 and increasing ROS production and reduce MMP. Ellagic acid (72) stimulates apoptosis through inhibition of the nuclear factor NF-κB [117]. Treatment of INS-1 and MIA PaCa-2 cells with hypoxoside (77) and hyperoside (78) isolated from *Hypoxis colchicifolia* (South Africa) leads to G2/M phase cycle arrest and caspase-3 acti-

vation in these cells. Resveratrol (67) isolated from *Commiphora africana* (Nigeria) has been used in several clinical trials [118]. Its mechanism of action relies not only on S-phase cell cycle arrest and survival inhibition, but also on activation of p53 protein, while inhibiting cyclooxygenase and cytochrome P450 enzymes [119]. The action of epigallocatechin gallate (68) isolated from *Camellia sinensis* (Morocco) on cancer cells is mainly based on cycle arrest and apoptosis phenomenon, through activation of caspase-3, caspase-9 and PARP-1 in MCF-7 cells. It also has an anti-metastatic activity by down-regulating the MMP-2, MMP-3 and MMP-9 proteins [120, 121].

Steroids

2"-Oxovoruscharin (79), isolated from *Calotropis procera* (Burkina Faso), shows anti-cancer effects against various cell lines (A549, Hs683, U373, HCT-15 and LoVo). It binds and inhibits the Na⁺/K⁺ ATPase complex, which results in modulation of different signaling cascades controlling proliferation mechanisms, apoptosis or gene expression [122]. β -sitosterol (80) has antitumor effects against several types of cancer including breast, cervical, prostate, colon and lung cancer [123]. Apoptosis occurs through the activation of caspases 3 and 9, by reducing the levels of Bcl2 and PI3K/Akt proteins, and by decreasing MMP. It also causes cell cycle arrest at S and G2/M phases [124, 125]. Two plants harvested in Northern Africa, *Calotropis procera* (Egypt) and *Trigonella foenumgraecum* (Morocco), used to isolate UNBS1450 (81) and diosgenin (82) respectively, show cytotoxic activity. UNBS-1450 (81) triggers apoptosis of U937 cells by cleavage of pro-caspases 8, 9, and 3/7, by reducing the expression of the anti-apoptotic protein Mcl-1, and by recruiting pro-apoptotic proteins Bax and Bak [126]. Diosgenin (82) isolated from *Trigonella foenumgraecum* (Morocco) increases the accumulation of p53 and p21 proteins that stop 1547 cells in the G1 phase [127].

Saponins

Saponins (85), (87) and (88), isolated from *Tetrapleura tetraptera*, *Ardisia kivuensis* Taton, *Raphia vinifera*, respectively (Cameroon), induce apoptosis of CCRF-CEM cells through the decrease of MMP, increase of ROS production and activation of caspases 3/7, 8 and 9. Olean-

12-en-3-O-D-glucopyranoside (85) and pro-genin III (88) block cell cycles at G0/G1 and G1 phases, respectively [128-130]. Daucosterol (86), isolated from *Crateva adansonii* (Cameroon), inhibits the proliferation of DU145 and PC-3 cells derived from prostate metastases by decreasing the levels of cdk1 and pcdk1, and leading to cycle arrest in G0/G1 phase cycle. In addition, the anti-apoptotic proteins Akt, p-akt and Bcl-2 are decreased, while the pro-apoptotic protein Bax is increased [131]. The combination of balanitin-6 (83) and -7 (84), extracted from *Balanite aegyptiaca* from Burkina Faso, promotes the depletion of intracellular [ATP], causing the disruption of the actin cytoskeleton and altering cell proliferation and migration of glioblastoma and lung cancer cells lines [132].

Organosulfur

Two organosulfur compounds, allicin (89) and S-allylcystein (90) isolated from the Moroccan plant *Allium sativum*, showed anti-cancer activity on HepG2 and A2780 cells, respectively [90]. Chu et al., showed that allicin (89) decreases cytoplasmic p53, PI3K/mTOR and Bcl-2 levels [133]. S-allylcystein (90) causes the G1/S phase arrest and induces apoptosis, accompanied by a decrease in pro-caspase-3, Parp-1 and Bcl-2, and an increase in active caspase-3 and Bax. S-allylcystin significantly decreases the accumulation of Wnt5a, p-AKT and c-Jun proteins, which are key proteins involved in proliferation and metastatic processes [134].

Opportunities for traditional or modern use of anti-cancer molecules

The use of anti-cancer molecules from African medicinal plants to treat cancer is accepted as part of a medical intervention. The main reasons for this acceptance are not only the small side effects induce by these molecules, but above all their relatively low cost and effectiveness against cancer cells. Many of African medicinal plants have the ability to fight a wide range of cancers, inhibiting enzymes involved in tumor development and with anti-proliferative effects. But, at the same time inducing antioxidant effects and repairing DNA damage of healthy cells [135]. Indeed, between 2002 and 2005, the World Health Organization adopted its first ever strategy to promote traditional medicine with the aim of reducing global

cancer mortality. This framework also aims to deepen the potential risks related to the active principles of plant extracts: the identification of secondary metabolites, the identification of mechanisms of action and the evaluation of safety [136]. Thus, in view of the growing interest of populations, especially African, for traditional medicines, the WHO has adopted its new strategy (2014-2023) for the treatment of diseases, especially chronic ones such as cancer. This strategy has two major objectives: (1) to support states seeking to leverage the contribution of traditional medicine to health, well-being and care; (2) promote the safe and effective use of traditional medicine through regulation of products, practices and practitioners [137]. Over the years, several studies have shown that some bioactive substances from the African flora are promising candidates for the development of new drugs. There are also many new cancer molecules currently in clinical development with good selectivity against cancer cell lines and molecular targets associated with cancer. In particular beta-sitosterol, betulinic acid, curcumin, resveratrol, lycopene, 2'-oxovoruscharine and UNBS1450 [99].

Our work thus found that the identification of isolated active biological extracts from endemic African plants is a rational approach to the development of new anti-cancer drugs. It is therefore necessary for researchers on the African continent to continue to work on identifying biomolecules that can treat cancer so that the most economically vulnerable population can easily access them. The strengthening of collaboration between research teams in all African regions must be accelerated in order to promote the identification of new molecules, their therapeutic and dosage targets and the anti-cancer mechanisms of action. This collaboration will ultimately lead technology transfer that is essential to sustain this biomedical research.

Key technologies and methods of synthetic biology research on medicinal natural products

Here, we have reviewed the complexity of essential oils from native African plant in terms of their metabolites, with potential applications as anticancer molecules. Given that, the high demand for plant medicinal products and at the same time the difficulties of cultivation, abundance of metabolites, purification and chemi-

cal synthesis need alternative methods of production of active compounds are necessary. Great progress with the use of host microorganisms has been made recently focusing on the production of complex plant-derivate molecules such as terpenoids using *Escherichia coli* [138] or *Saccharomyces cerevisiae* [139]. However, the use of engineering in host microbes still represents a challenge due to the introduction of plant-derived genetics and metabolic machinery, as well as the potential that the product be toxic to the host.

In this direction, plants synthetic biology allows the sustainable production of phytochemicals by a direct isolation of molecules from plant resources. The use of plant platforms, whether at the cellular level (cell cultures), tissues (hairy root culture) or from whole plant, provides greater cost-efficiency for the production of phytochemicals, thanks to i) quick and easy cultivation not affected by environmental factors; ii) efficient energy dependence in terms of sources of carbon, light, water, and essential nutrients; iii) the similarity of metabolic pathways and genetic machinery between plants; iv) the use of different root, stem or leaf tissues would facilitate the production of natural products; v) the use of combinatorial engineering strategies (overexpression of enzymes, tissue-specific production of metabolites) that can be used to enhance the production and isolation of specific metabolites.

Efficiency in plant cell culture and synthetic biology has already been demonstrated for the production of natural products in the cosmetic, food, and pharmaceutical industries [140-142]. Besides, general strategies to enhance plant metabolite production have recently been reviewed in [143].

A good example of this is the use of the tobacco plant or *Nicotiana benthamiana* which, through the expression of different genes of interest, has allowed the production of alkaloids, terpenoids, flavonoids and phenolic derivatives [144-151], which are metabolites enriched in essential oils.

It is still a big challenge to use plant synthetic biology for the production of high value essential oil. Mainly because the knowledge on the production processes of these compounds by plants is very scarce. In the same way, the intro-

duction of complex enzymatic systems would activate regulatory mechanisms, at the genetic and metabolic levels that could interfere or alter the structure of the molecules that are required to be produced by plant engineering [152, 153].

Recently new tools of genome editing by CRISPR method have been applied for gene edition in plants showing great efficiency [154, 155]. Which will allow a rapid advance in the generation of molecules and natural products by plants biology synthetic.

Conclusion

Compounds isolated from African medicinal plants clearly constitute a promising source of powerful anticancer agents. This review summarizes the data obtained on molecules identified in the literature as potential pharmacological agents, focusing on their mechanisms of molecular action. Although some of anti-cancer compounds described in this review are already in clinical trials, most of them should be further investigated to prove their effectiveness and to explore their potential in combination therapies, especially to find ways to overcome resistance to conventional drugs. Considering the diversity of African medicinal plants and the efficacy of their molecules, it is imperative that researchers around the world, and particularly those on the African continent, continue to work on identifying bioactive molecules usable in cancer treatment.

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