Chapter 1

African Plants with Antiproliferative Properties

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Additional information is available at the end of the chapter

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Abstract

Plant-derived compounds have been an integral component in man's quest to discover ideal anticancer agents. A number of new agents are currently in clinical development with promising selective activity against cancer cell lines and cancer-related molecular targets. This book chapter discusses 14 of such compounds isolated from African plants from 15 plant families. Also contained in this book chapter are compounds from African plants that hold prospect as potential anticancer agents as informed by their *in vitro* and *in vivo* preclinical studies. It is, therefore, worthwhile that researchers in the African continent and the world over should keep on working on identifying biomolecules with potential in cancer management.

Keywords: African plants, antiproliferation, clinical trials, preclinical studies, cancer

1. Introduction

Plant-derived compounds have been an important source of several clinically useful antiproliferative agents in the past half century [1, 2]. Compounds of natural origin such as vinblastine, vincristine, topotecan and irinotecan, etoposide, and paclitaxel have been some of the chemotherapeutic agents still in clinical practice. A number of new agents are currently in clinical development with promising selective activity against cancer cell lines and cancer-related molecular targets, while some agents that failed in earlier clinical studies are stimulating renewed interest.

The present chapter will consider plant-derived antineoplastic single chemical entities currently in clinical trials as oncology drugs. Lead compounds from plants showing promising

in vivo antiproliferative activity will also be discussed in terms of their origin, possible mechanism of action, and their potential use in cancer management. Most importantly, natural products are generally believed to possess therapeutic potentials hence mostly pharmacologically relevant. This is coupled with the belief that they hold a significant advantage of them being the safer alternative to synthetic molecules [3–5].

Natural products hold a convincing prospect in the continual search for effective anticancer agents with tolerable side effect profile. These observations are well articulated in reviews that have unearthed the fact that about 47% of new anticancer agents that have been approved up to 2006 were either a natural product or their derivative [6]. Due to the labor-intensiveness of bioassay-guided isolation of natural products from crude extracts, more pharmaceutical firms tend to resort to a rapid high-throughput screening of molecular target-based pure compound chemical libraries. Nevertheless, the importance of identification of these bioactive molecules from natural origin is still very palpable in recent years with industries adopting screening procedures that maximize their output [7–9].

A substantial number of chemical moieties of plant origin are currently in various stages of clinical trials [10–12]. However, most of these plant-derived biomolecules are derived from the anticancer agents in clinical therapy which include paclitaxel [ABI-007, RPR-116278A, XRP9881 (RPR109881A)], camptothecin [exatecan mesylate, orathecin], vinblastine and vincristine (vinflunine ditartrate, vinorelbine, anhydrovinblastine, vincristine sulfate TCS), and epipodophyllotoxin (NK-611 and tafluposide 105) [10–12]. Such newer molecules based on the structures of these anticancer agents were not discussed in this book chapter. However, newly isolated compounds from African plants which show potential as possible anticancer agent based on their *in vivo* and *in vitro* studies were included in this book chapter.

2. Compounds of plant origins currently under clinical trial as potential anticancer drugs

2.1. Betulin, β-sitosterol, and betulinic acid

Parinari curatellifolia Planch. ex. Benth (Chrysobalanaceae) is a plant found widely distributed in Africa. Traditionally, it is used for the treatment of toothache (root infusion), pneumonia (hot fomentation of the bark), fevers (leaf decoction), and also as dressing agents for fractures, dislocations, wounds, sores, and cuts (crushed leaves) [13]. In Northern Nigeria, traditional healers use it for the treatment of cancer. Research has indicated that the bioactive constituents of the plant can decrease cancer risk through their antioxidant, antitumorigenic, and antimicrobial activity as well as their ability to directly suppress carcinogen bioactivation. Betulinic acid has been shown to be cytotoxic to neuroectodermal and brain tumor cells [14]. Its apoptotic property is through the regulation of the intrinsic pathway by changing mitochondrial membrane potential and activation of p38 MAPK and SAP/JNK by initiating reactive oxygen species (ROS) generation [15]. This compound can be semisynthesized by oxidation of betulin, which occurs more abundantly [16]. A betulinic acid-containing ointment is undergoing

Phase I/II clinical evaluation for the treatment of dysplastic nevi with moderate to severe dysplasia [17]. Halilu et al. after preliminary investigations also revealed that betulin, β-sitosterol, and betulinic acid were toxic to the cervical epithelial carcinoma (HeLa) cell line used in the assay using the XTT colorimetric assay and cell proliferation Kit II [18].

2.2. Curcumin (diferuloylmethane)

Curcumin, a polyphenol obtained from turmeric (*Curcuma longa* L., Family: Zingiberaceae), has been associated with a wide range of activities including potential antitumor effect, antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory effect [19]. Turmeric plant is very common in Asia and Africa [20]. The plant is employed in traditional medicine for treating a wide range of communicable and noncommunicable diseases such as skin infections, worm infestations, diabetes, liver diseases, and gallstones [21]. A phase II clinical trial of curcumin in patients with advanced pancreatic cancer showed a brief but significant tumor regression with no toxicities observed. Also, clinical studies of curcumin alone or in combination with other chemotherapeutic agents (gemcitabine, 5-fluorouracil, and oxaliplatin) have been carried out in the United States and Israel for patients with colorectal and pancreatic cancers [22]. The mechanism of action was shown to be possibly due to its ability to downregulate expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), cyclooxygenase-2 (COX-2), and phosphorylated signal transducer and activator of transcription 3 (STAT3) in peripheral blood mononuclear cells. However, absorption was observed to be poor [22].

2.3. Lycopene

This compound is present in fruits and vegetables, notably *Solanum lycopersicum* L. (Solanaceae) and its processed products [23]. *Solanum lycopersicum* is widely distributed in Africa. It is used in folk medicine for treating burns, wounds, and toothaches. Nahum et al. reported that lycopene inhibits cell cycle progression via reduction of the cyclin D level and retention of p27 in cyclin E-cdk2, thus leading to inhibition of G1 CDK activities in breast and endometrial cancers [24]. Besides its antioxidant and anti-inflammatory activities, lycopene has been established to possess anticancer property in both *in vitro* and *in vivo* models. Its mechanism of action has been established to be via the activation of the electrophile/antioxidant response element (EpRE/ARE) transcription system, inducing the expression of phase II detoxifying enzymes, and arresting the cell cycle at the G0/G1 phase by regulating cyclin D1 and the PI3K/Akt pathway [25]. Lycopene is currently in Phase II clinical trials in the United States for the prevention and treatment of prostate cancer [26].

2.4. Resveratrol

Resveratrol (3,4,5-trihydrostilbene) is a phenolic compound found in several plants such as *Vitis vinifera* L. (Vitaceae), *Morus alba* L. (Moraceae), and *Arachis hypogaea* L. (Fabaceae). *A. hypogea* and *M. alba* are widely distributed in Africa. It is used in the treatment of infectious diseases. The cardioprotective property of red wine has been attributed to resveratrol [27, 28].

A number of studies have reported on the antioxidant, anti-inflammatory, anticancer, and anti-aging activities of resveratrol [27–29]. Its mechanism of action entails the enhancement of apoptosis by acting at multiple cellular targets, including activation of p53, inhibiting cyclooxygenase and cytochrome P450 enzymes, and activating AMP-activated kinase (AMPK) [27–29]. Also, it exhibits sensitization effects on drug-resistant tumor cells and results in a synergistic cytotoxicity when combined with established anticancer therapies [30]. This compound is now undergoing Phase I/II clinical trials for the prevention and treatment of colon cancer in the United States [31].

2.5. 2″-Oxovoruscharin and UNBS1450

From *Calotropis procera* (Aiton) W.T. Aiton (Asclepiadaceae) is isolated the cardenolide, 2″-oxovoruscharin with a demonstrated *in vitro* antitumor and Na+/K+-ATPase inhibitory activities [32]. *Calotropis procera* is native to North Africa, Tropical Africa, Western Asia, South Asia, and Indochina [33]. Reduction of the formyl group in the 2″-oxovoruscharin molecule into a hydroxymethyl group yields UNBS1450 with an improved *in vitro* cytotoxicity profile when compared with the parent compound [34]. UNBS1450 has been established to induce the disruption of the actin cytoskeleton to affect multiple signaling pathways by binding to the sodium pump, and that leads to nonapoptotic cell death [35]. UNBS1450 has entered Phase I clinical studies in Europe for patients with solid tumors and lymphomas [36]. *Calotropis procera* is widely distributed in Africa and also employed in folkloric medicine as an abortifacient, hepatoprotective agent, anti-inflammatory agent as well as treating leprosy, syphilis, and cutaneous infections [37].

2.6. Combretastatin A1 and combretastatin A4

Combretastatins isolated from the South African tree, *Combretum caffrum* Kuntze (Combretaceae) are simple stilbenoid compounds with a number of activities including anticancer activity. The A series combretastatin are cis-stilbenes with potent *in vitro* antiproliferative activity against the leukemic P388 and L1210 cell lines. Combretastatin A4, the most potent member of the group, in sodium phosphate prodrug form, has not long ago completed phase I clinical trials as an anti-angiogenic tubulin-binding agent and in nonsmall cell lung cancer and cervix carcinoma, and is presently being assessed in a phase II trial with regards to ovarian, anaplastic thyroid, gastric, and other solid tumors [19, 38]. A propanamide derivative of combretastatin A4 exhibits even more potent antitumor effect than the phosphate by inducing an irreversible blockage of tumor blood flow and is now in phase I clinical studies in Europe and the United States [39, 40]. Again, a bisphosphate prodrug of combretastatin A1 has also been reported to be more potent than combretastatin A4 phosphate and is undergoing phase I anticancer clinical trials in the United Kingdom [40].

2.7. Perillyl alcohol

The essential oils of *Lavandula X intermedia* (Lamiaceae) and *Prunus avium* L. (Rosaceae) are rich in perillyl alcohol, a monoterpenoid with a monocyclic carbon skeleton [41]. *Lavandula*

X intermedia and *Prunus avium* are plants which are widely distributed in South and North Africa, respectively. *In vitro* studies have established the cytotoxicity of perillyl alcohol to cell lines derived from lung cancer, pancreatic cancer, prostate cancer, breast cancer, and leukemia. *In vivo* studies also revealed the inhibitory effects of perillyl alcohol against UVB-induced skin carcinogenesis and DMBA-induced murine melanoma models [42, 43]. Its antiproliferative activity was shown to be due to its arrest of the G0/G1 phase, by modulating the protein levels of cyclin-dependent kinases and cyclin-dependent kinase inhibitors [44]. Currently, perillyl alcohol is undergoing phase I/II clinical trials in patients with breast cancer, ovarian cancer, and glioblastoma multiform [45].

2.8. Alvocidib (Flavopiridol)

Alvocidib, a semisynthetic rohitukine, is an N-methylpiperidine alkaloid first isolated from *Aphanamixis polystachya* (Roxb.) Wight & Arn. (Meliaceae) and later from the African plant *Schumanniophyton magnificum* (K.Schum.) Harms. (Rubiaceae) [46]. It is also present in the stem bark of *Dysoxylum binectariferum* Hiern (Meliaceae) from India and documented to have immunomodulatory and anti-inflammatory activity [46, 47]. Alvocidib has been established to exhibit cytotoxicity for a wide range of cancer cell lines and has demonstrated *in vivo* activity against prostate cancer, head and neck cancer, hematopoietic neoplasia, leukemia, and lymphoma xenograft murine models [48, 49]. Its mechanism has been established to involve inhibition of cyclin-dependent kinases (CDKs) by competing with adenosine triphosphate (ATP) at their nucleotide binding sites and causes cell cycle arrest at either the G1 or G1/M phases. Also, it exhibits apoptosis induction, and antiangiogenic and antiproliferative effects, by interacting at other target sites besides CDK [50, 51]. Alvocidib is the first cyclin-dependent kinase inhibitor in clinical trials for the treatment of patients with non-Hodgkin's lymphoma, renal, prostate, colon, and gastric cancers [50–53].

2.9. Maytansinoids

The parent nitrogen-containing macrocylic substance, maytansine, was first isolated by Kupchan and colleagues from the Ethiopian shrub *Maytenus serrata* (Hochst. ex A. Rich.) R. Wilczek (Celastraceae) [54]. Maytansinoids exhibits antimitotic activity due to tubulin binding hence resulting in inhibition of microtubule assembly [55, 56]. However, there is an overlap of maytansinoids with vincristine in their binding site activity [57, 58]. Maytansinoids has exhibited antiproliferative activity against Lewis lung carcinoma, B-16 melanocarcinoma, murine solid tumor test system, and antileukemic activity against P-388 lymphocytic leukemia, significantly over a 50–100 fold dosage range at the μg/kg level [54, 59]. Clinical trials with maytansine, both alone and as a monoclonal antibody conjugate, however, showed toxicity as well as low response rates in adults with advanced cancer [12, 31, 60]. This informed further metabolic studies involving maytansine to be undertaken to produce analogs with better clinical potential [61]. The extremely high *in vitro* potency of the maytansinoids has sustained interest in structure-activity relationship studies, analog development, total synthesis, and preclinical studies [62].

2.10. Indirubin and 1-methylisoindigo

These are indole alkaloids isolated from the leaves and/or stems of several plants which include the African plant, *Indigofera tinctoria* L. (Fabaceae), as well as *Baphicacanthus cusia* (Nees) Bremek. (Acanthaceae), *Indigofera suffruticosa* Mill. (Fabaceae), *Isatis tinctoria* L. (Brassicaceae), and *Polygonum tinctorium* Ait. (Polygonaceae) [63, 64]. Indirubin has been demonstrated to exert its antileukemic effect by competing with ATP for binding to the catalytic subunit of cyclin-dependent kinase (CDK), via hydrogen bonding, leading to the inhibition of this enzyme [65]. 1-Methylisoindigo is a derivative developed to improve water solubility and other pharmaceutical properties of indirubin. 1-methylisoindigo exhibited significant anticancer activity through a multitargeting profile including inhibition of DNA biosynthesis and assembly of microtubules, induction of cell differentiation, and down-regulation of c-myb gene expression [65, 66]. 1-Methylisoindigo is under clinical trial in the People's Republic of China for chronic myelogenous leukemia (CML) [67].

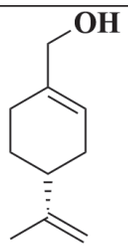
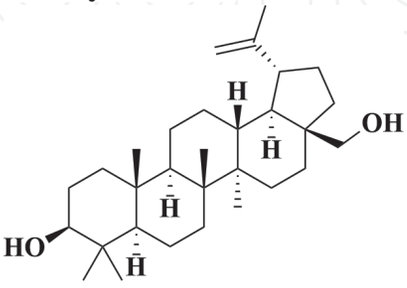
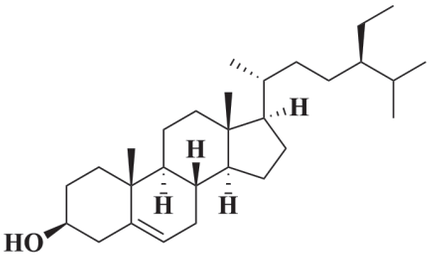
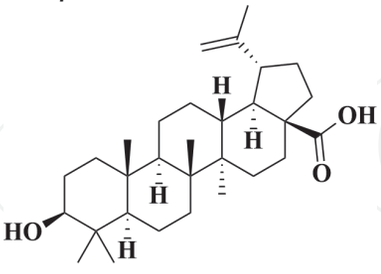
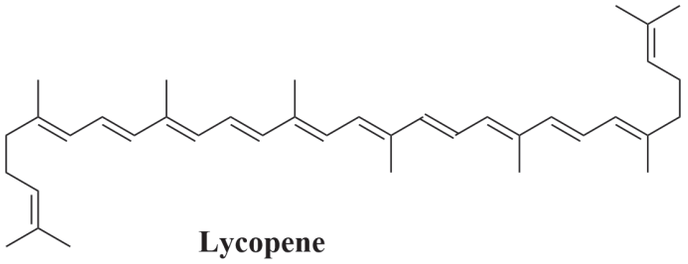
3. Plant-derived compounds with potential anticancer activity but not yet in clinical trials

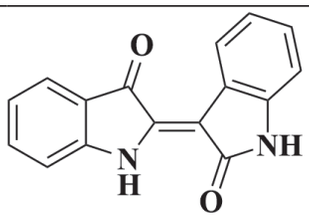
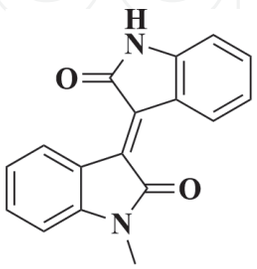
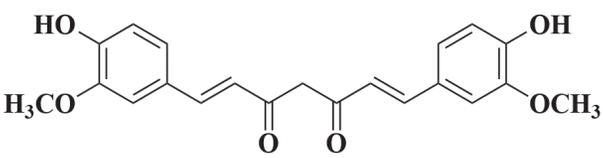
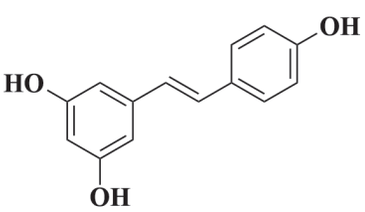
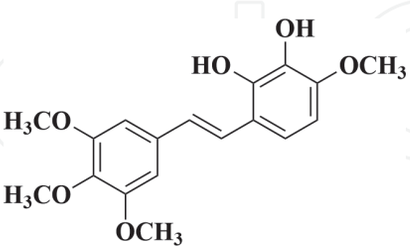
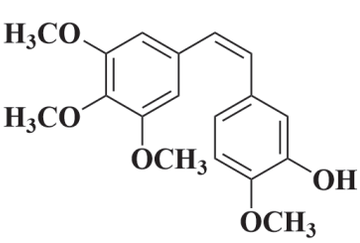
3.1. Fagaronine

Fagaronine is a benzophenanthridine alkaloid isolated from *Fagara zanthoxyloides* Lam. (syn. *Zanthoxylum zanthoxyloides*) (Rutaceae), which is widely distributed in Uganda and some other African countries. The root bark extract of the plant is used in the treatment of elephantiasis, malaria, dysmenorrhoea, impotence, and abdominal pain. Fagaronine exhibits antitumor activity against P388 and L1210 murine leukemic cell lines. Its mechanism of action is via inhibition of DNA and RNA polymerase activities as well as inhibition of protein synthesis. This results in disruption of replication in rapidly dividing neoplastic cells. Again, there has been observed inhibition of reverse transcriptase by fagaronine (**Tables 1** and **2**) [68, 69].

3.2. Isofuranonaphthoquinone

Isofuranonaphthoquinone is a phytochemical constituent that occurs in *Bulbine* species (Asphodelaceae) such as *Bulbine abyssinica* A. Rich., *Bulbine capitata* Poelln., and *Bulbine frutescens* (L.) Willd., which are found in Australia and southern Africa. Traditionally, *Bulbine frutescens* is used for a wide range of skin conditions including acne, burns, blisters, cold sores, cracked lips, fingers, nails and heels, insect bites, fever blisters, mouth sores, sunburn, and ringworm among others. It is used internally for coughs, cold, and arthritis. Cell viability assay was used to investigate the action of isofuranonaphthoquinone found in *Bulbine frutescens* on Jurkat T cells [70]. In this study, it was concluded that the effect of isofuranonaphthoquinone was comparable to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), an anticancer agent, and its effects were irreversible. The study showed that isofuranonaphthoquinone could be exerting its activity by generating reactive oxygen species which result in cell death and that it inhibits drug efflux pumps which have been implicated in drug resistance in cancer cells. A combination with BCNU

Class of compounds	Structure	References
1. Terpenoids		
– **Monoterpenes**	 **Perillyl alcohol**	**[41–45]**
– **Triterpenes**	 **Betulin**	**[18]** **[18]**
– **Tetraterpene**	 **β-sitosterol**	**[14–18]**
	 **Betulinic acid**	**[24–26]**
	 **Lycopene**	

Class of compounds	Structure	References
2. Alkaloids		
– **Indole**	 **Indirubin**	**[63–65]**
	 **1-methylisoindigo**	**[63–67]**
3. Polyphenols		
– **Diarylheptanoid**	 **Curcumin**	**[22]**
– **Stilbenoid**	 **Resveratrol**	**[27–31]**
	 **Combretastatin A1**	**[40]**
	 **Combretastatin A4**	**[19, 38–40]**

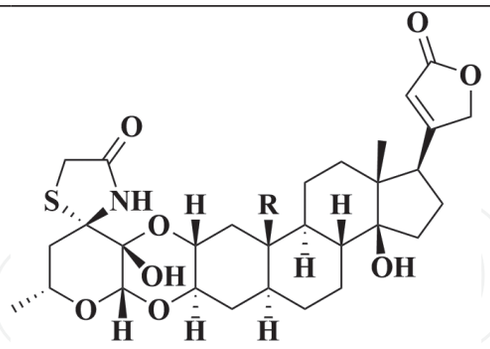
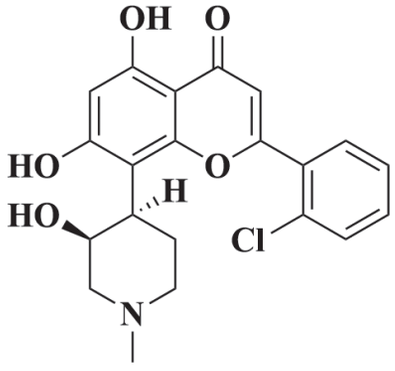
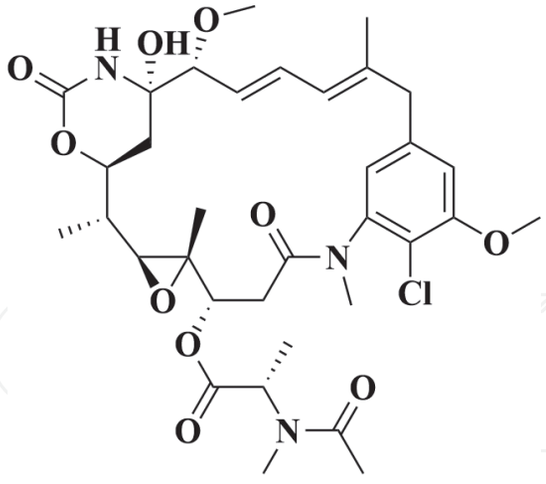
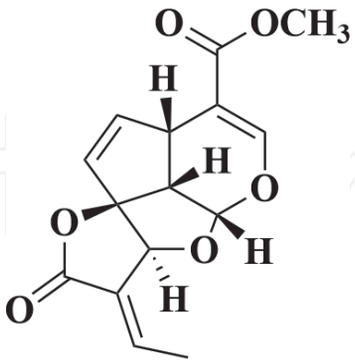
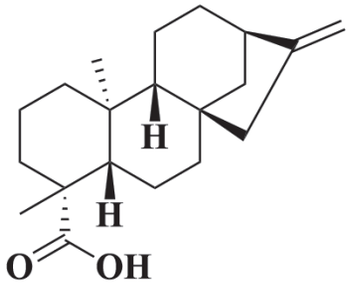
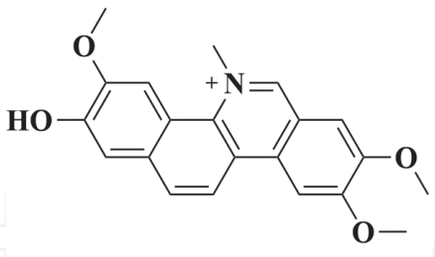
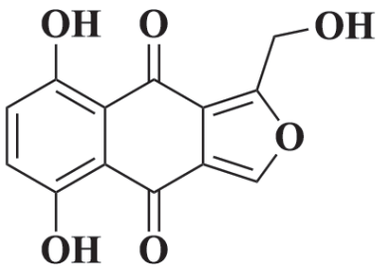
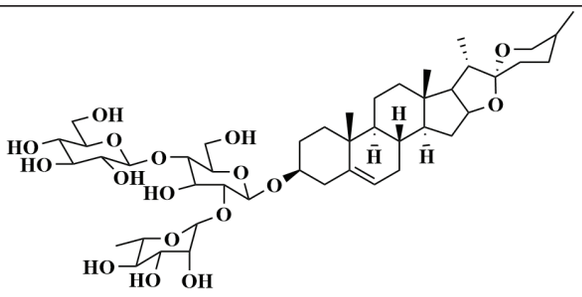
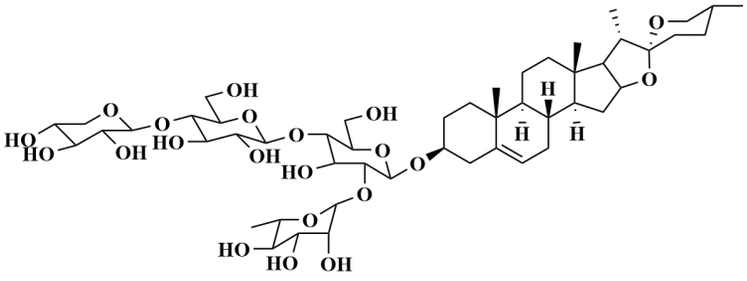
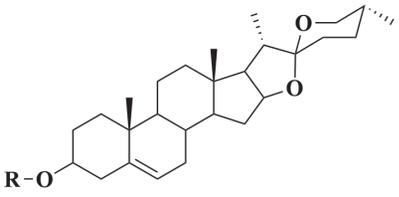
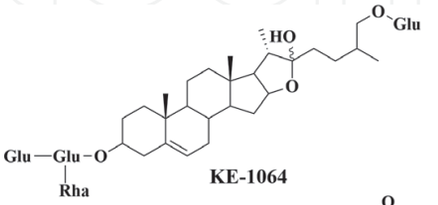
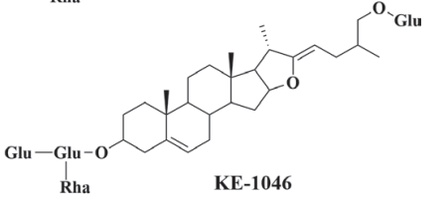
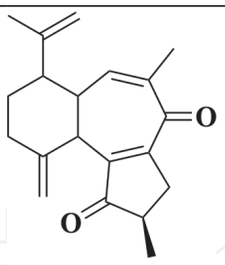
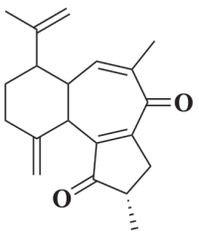
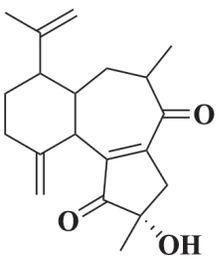
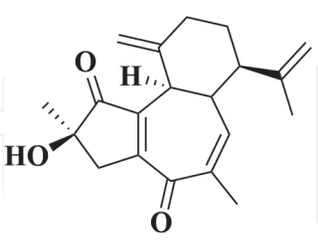
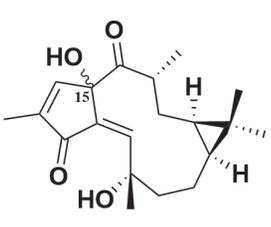
Class of compounds	Structure	References
4. Steroids		
– **Cardenolides**		[32–37]
	2"-oxovoruscharin **R = CHO**	
	UNBS1450 **R = CH_2OH**	
5. Flavoalkaloid		[46–53]
	Alvocidib	
6. Maytansinoids		[12, 31, 54–62]
	Maytansine	

Table 1. Plant-derived compounds currently under clinical trial as anti-cancer drugs.

showed greater toxicity effects on the Jurkat T cells than the individual compounds. Thus, this compound is a potential lead candidate for anticancer drug development and an adjunct compound in combination treatment regimens [70].

Class of compounds	Structure	References
1. Terpenoids		
– **Monoterpenes**		
• **Iridoid lactone**	 **Plumericin**	**[72]**
– **Diterpenes**		**[76]**
• **Kaurane**	 **Kaurenoic acid**	
2. Alkaloids		
– **Benzophenanthridine**	 **Fagaronine**	**[68, 69]**
3. Quinones	 **Isofuranonaphthoquinone**	**[70]**

Class of compounds	Structure	References
4. Saponins		[74]
	Balanitin-6	
		[74]
	Balanitin-7	
5. Steroids		
	SAP-1016 R = Glu—Glu—Xyl (Rha)	
	SAP-884 R = Glu—Glu (Rha)	[73]
	Spirostanes	
		
	KE-1064	
		[73]
	KE-1046	
	Furostanes	

Class of compounds	Structure	References
6. Crotophorbolanes	 **Curcusone A**	[75]
	 **Curcusone B**	[75]
	 **Curcusone C**	[75]
	 **Curcusone D**	[75]
	 **4Z-jatrogrossidentadion** **15β- OH** **15-epi-4Z-jatrogrossidentadion** **15α- OH**	[75]

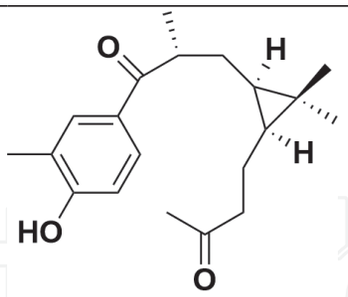
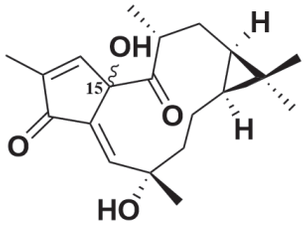
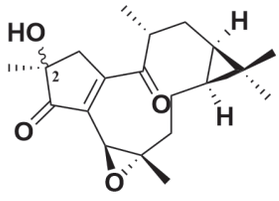
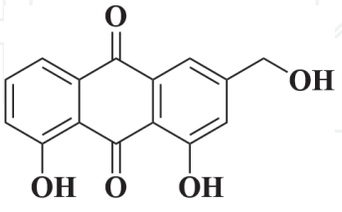
Class of compounds	Structure	References
	 Multidione	[75]
	 4E-jatrogrossidentadion 15β- OH	[75]
	 12-epi-hydroxyisojatrogrossidion 2β- OH 2-hydroxyisojatrogrossidion 2α- OH	[75]
7. Anthraquinone	 Aloe-emodin	[77–79]

Table 2. Plant-derived compounds with potential anti-cancer activity but not yet in clinical trials.

3.3. Plumericin

Momordica charantia L., (Cucurbitaceae) is a plant commonly known as bitter gourd or bitter melon which is widely distributed in Asia and tropical Africa. Bitter gourd extracts have

been shown to have antioxidant, antimicrobial, antiviral, antihepatotoxic, hypoglycemic, and antiulcerogenic properties [71]. It has also been shown to have anticancer properties. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay was used in this experiment to investigate the antiproliferative activity of plumericin, isolated from this plant. The results indicated it to have high antiproliferative effect against leukemia (NB4 and K562), breast cancer (T47D) cell lines, and a moderate activity against liver cancer cell line (C3A) [72].

3.4. Balanitin-6 and balanitin-7

Balanites aegyptiaca Del (Balanitaceae) is a spiny evergreen tree found in the dry regions of the Middle East, Africa, and Southern Asia. [73]. Traditionally in Egypt, the fruits are used as antidiabetic agents. In Sudan, it is used in the treatment of jaundice and as an anthelminthic. Additionally, the extracts have been shown to show abortive and antiseptic characteristics [74]. A study was conducted to further characterize the anticancer activity of the steroidal saponins of *B. aegyptiaca* kernels, which contain a mixture of Balanitin-6 (28%) and balanitin-7 (72%). The mixture was found to display greater antiproliferative activity than oxaliplatin as well as etoposide against human cancer cell lines U373 glioblastoma and A549 nonsmall cell lung cancer, though it was less active compared to taxol. The results also showed that the balanitin-6, balanitin-7 mixture is more cytotoxic than it is cytostatic. Its antiproliferative activity does not appear to be by inducing apoptotic cell death and it does not appear to induce detergent-like effects on the cells tested in the study. Rather, its *in vitro* activities are indicated to be at least partially as a result of ATP depletion, the result of which is considerable disorganization of the actin cytoskeleton, finally leading to impaired cancer cell proliferation and migration. Additionally, the study showed that the mixture does not cause intracellular reactive oxygen species levels to increase, unlike a number of anticancer agents of natural origin. In *in vivo* studies, the extent of increase of survival time reported for vincristine was found to be the same for the mixture when tested on mice bearing murine L1210 leukemia grafts. The preliminary *in vivo* results obtained showed that new hemi synthetic derivatives of balanitin-6 and -7 which have enhanced *in vivo* and *in vitro* anticancer activity coupled with decreased toxicity could possibly be produced, which would markedly improve the therapeutic ratio of these compounds [74].

3.5. Spirostanes and furostanes

Another study used the MTT assay to evaluate the antiproliferative activity of furostane (KE-1046 and KE-1064) as well as spirostane (SAP-1016 and SAP-884) saponins isolated from *Balanites aegyptiaca* Del. Potent antiproliferative activity was observed for SAP-1016 against HT-29 human colon and MCF-7 human breast cancer cells. Additionally, for furostane saponins, there was considerable selectivity in growth inhibition between HFF normal cells and MCF-7 breast cancer cells. It was shown that SAP-1016 works by generation of reactive oxygen species in a time-dependent manner in both MCF-7 and HT-29 cancer cells. It also induced apoptosis through the activation of caspase-3 in HT-29 cells [73].

3.6. Curcusones

Found in Africa and Asia, *Jatropha curcas* L. (Euphorbiaceae) is a large drought-resistant shrub, which is used for multiple purposes. The seeds and the oil obtained from them are used for

biodiesel production, as a cure for syphilis, and also as a purgative. Different forms of this plant are used in West Africa to treat ailments such as jaundice, mouth sores as well as sores due to guinea worm infestation, fever, and joint rheumatism. The crushed leaves and the latex show antiparasitic activity as well as antibacterial activity against Staphylococcus aureus. Extracts of the stem have been suggested to have anti-insect, anti-inflammatory, cytotoxic, and molluscicidal activities. The MTT method was used to determine the anticancer activity of curcusone A, B, C, and D, pure compounds obtained from the stem of this plant. Curcusone A and B were revealed to possess antiproliferative activity with curcusone B, additionally, suppressing the metastatic process effectively at nontoxic doses. Curcusone C and D were shown to be active against L5178y mouse lymphoma cells. 2-Epi-hydroxyisojatrogrossidion, 4Z-jatrogrossidentadion, 2-hydroxyisojatrogrossidion, 4E-jatrogrossidentadion, and Multidione, 15-epi-4Z-jatrogrossidentadion have also been reported to exhibit potent cytotoxic activity against HeLa human cervix carcinoma cells and L5178y mouse lymphoma cells but exhibited no or low activities against the neuronal cell, PC12 [75].

3.7. Kaurenoic acid

Annona senegalensis Pers. (Annonaceae), (popular names: African custard apple or wild custard apple) has been reported to possess cytotoxic and anticancer effects. Kaurenoic acid, a diterpenoid, has been shown to have anticonvulsant, anti-inflammatory as well as antimicrobial properties. A cytotoxicity assay on Kaurenoic acid was performed using the MTT assay method against Henrietta Lack's cervical (HeLa) and pancreatic tumor (PANC-1) cell lines. Okoye et al. reported that kaurenoic acid exhibited better cytotoxic and antiproliferative activity against HeLa cells, than PANC-1 cells [76]. The anticancer effect of kaurenoic acid on breast, leukemia, and colon cancer cells has been documented, as well as activity on human glioblastoma, murine, and human melanoma cell lines. Terpenoids have been shown to exhibit antitumor activities by inducing apoptosis in various cancer cells by activating various pro-apoptotic signaling cascades and by the inhibition of metastatic progression and tumor-induced angiogenesis. Thus, kaurenoic acid, a terpenoid can potentially be further studied for its potential anticancer activity [76].

3.8. Aloe emodin

Aloe emodin is an anthraquinone compound found in many medicinal plants including the widely grown *Aloe vera* L. and *Rheum palmatum* L. (Rhei rhizome), used in traditional medicine in China and Africa. Previous studies report that aloe emodin has laxative, antibacterial, antiviral, antifungal, and hepatoprotective properties [77]. A recent study has shown that it possesses *in vivo* and *in vitro* antineuroectodermal tumor activity [78]. Another study indicated that aloe emodin showed inhibition of cell proliferation as well as induction of apoptosis in both Hep 3B and Hep G2 human liver cancer cell lines but through different antiproliferative mechanisms. p53 expression was induced in Hep G2 cells, along with a cell cycle arrest in the G1 phase. Added to this, there was a considerable increase in Bax and FAS/APO1 receptor expression. In the Hep 3B cells, the antiproliferative activity was in a p21-dependent manner which did not lead to cell cycle arrest or rise in Fas/APO1 receptor level. Rather, aloe emodin induced apoptosis was promoted through enhanced Bax expression. As a result, aloe emodin may be instrumental in preventing liver cancer [79].

4. Conclusion

A sizeable number of plant-derived compounds are currently under clinical trial for the management of cancers though much needs to be identified. This goes a long way to affirm the therapeutic benefits plants hold. It is therefore prudent that scientist and researchers in Africa and the world as a whole to continue to work on identifying newer compounds of natural origin that would hold potential in the management of cancers.

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