

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# African Plants with Antiproliferative Properties

---

Newman Osafo, Yaw Duah Boakye,  
Christian Agyare, Samuel Obeng,  
Judith Edem Foli and  
Prince Amankwaah Baffour Minkah

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.68568>

---

## 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, $\beta$ -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,  $\beta$ -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 down-regulate expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), 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. hypogaea* 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<sup>+</sup>/K<sup>+</sup>-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 *Schumanniohyton 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 macrocyclic 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 antimetabolic 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  $\mu\text{g}/\text{kg}$  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-methylisindigo

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-Methylisindigo is a derivative developed to improve water solubility and other pharmaceutical properties of indirubin. 1-methylisindigo 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-myc gene expression [65, 66]. 1-Methylisindigo is under clinical trial in the People's Republic of China for chronic myelogenous leukemia (CML) [67].

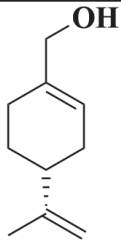
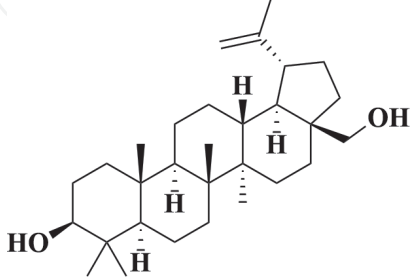
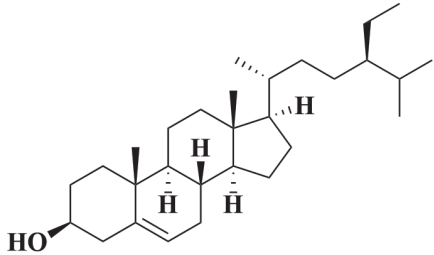
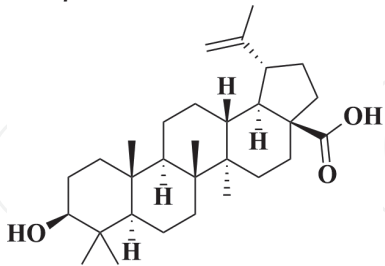
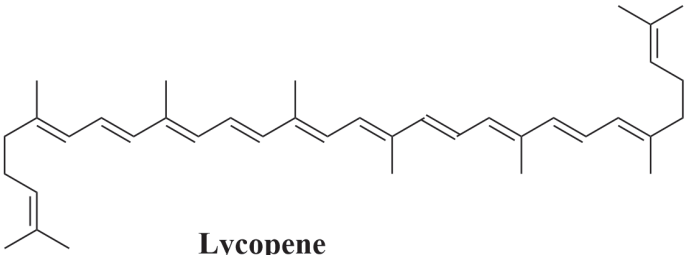
## 3. Plant-derived compounds with potential anticancer activity but not yet in clinical trials

### 3.1. Fagaronine

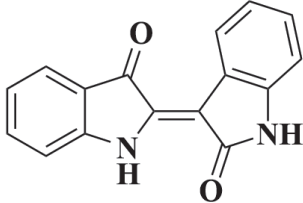
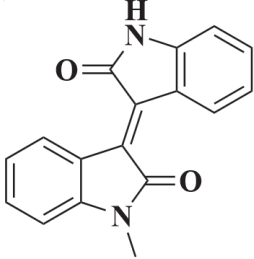
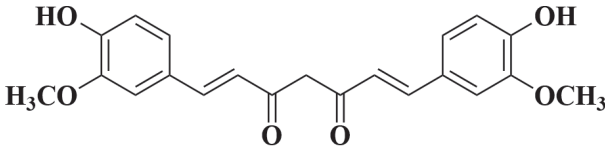
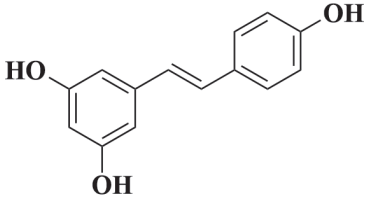
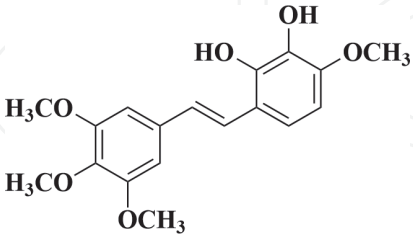
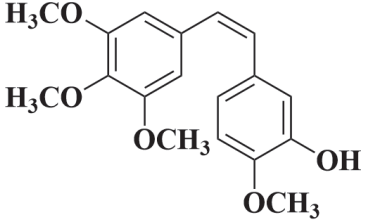
Fagaronine is a benzophenanthridine alkaloid isolated from *Fagara zanthoxyloides* Lam. (syn. *Zanthoxylum zanthoxyloides*) (Rutaceae), which is widely distributed in Uganda and some other African countries. The root bark extract of the plant is used in the treatment of elephantiasis, malaria, dysmenorrhoea, 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].

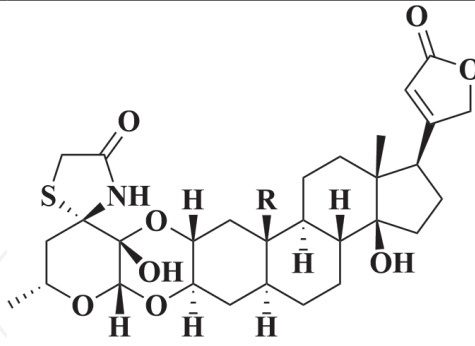
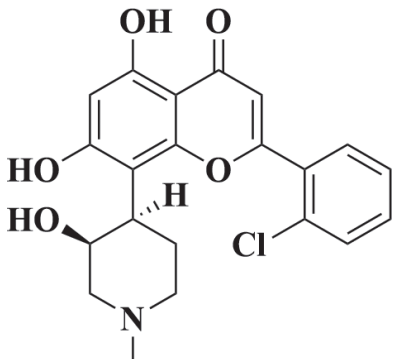
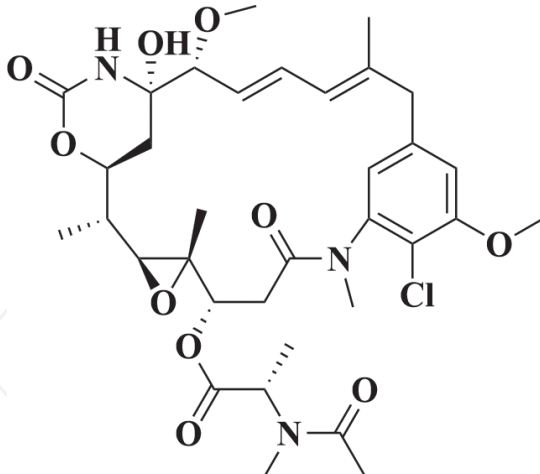
### 3.2. Isofuranonaphthoquinone

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	 <p><b>Perillyl alcohol</b></p>	[41-45]
- Triterpenes	 <p><b>Betulin</b></p>	[18]
- Tetraterpene	 <p><b><math>\beta</math>-sitosterol</b></p>	[14-18]
	 <p><b>Betulinic acid</b></p>	[24-26]
	 <p><b>Lycopene</b></p>	

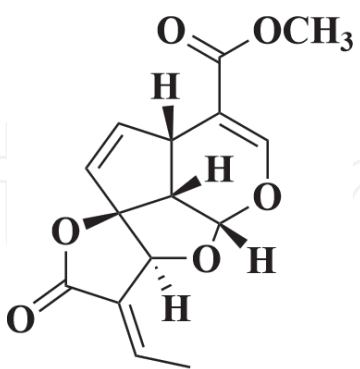
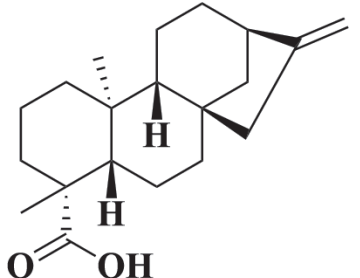
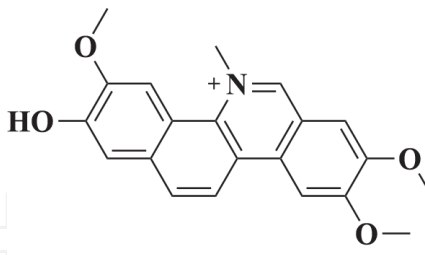
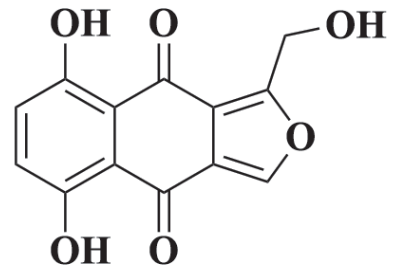


Class of compounds	Structure	References
2. Alkaloids		
- Indole	 <p style="text-align: center;"><b>Indirubin</b></p>	[63–65]
	 <p style="text-align: center;"><b>1-methylisoidigo</b></p>	[63–67]
3. Polyphenols		
- Diarylheptanoid	 <p style="text-align: center;"><b>Curcumin</b></p>	[22]
- Stilbenoid	 <p style="text-align: center;"><b>Resveratrol</b></p>	[27–31]
	 <p style="text-align: center;"><b>Combretastatin A1</b></p>	[40]
	 <p style="text-align: center;"><b>Combretastatin A4</b></p>	[19, 38–40]

Class of compounds	Structure	References
4. Steroids - Cardenolides	 <p>2''-oxovoruscharin R = CHO  UNBS1450 R = CH<sub>2</sub>OH</p>	[32-37]
5. Flavoalkaloid	 <p><b>Alvocidib</b></p>	[46-53]
6. Maytansinoids	 <p><b>Maytansine</b></p>	[12, 31, 54-62]

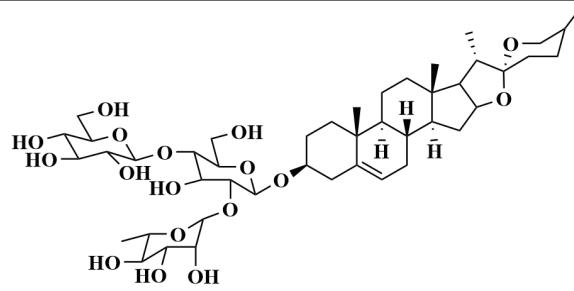
**Table 1.** Plant-derived compounds currently under clinical trial as anti-cancer drugs.

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		[72]
	<b>Plumericin</b>	
- Diterpenes		[76]
• Kaurane		
	<b>Kaurenoic acid</b>	
2. Alkaloids		
- Benzophenanthridine		
		[68, 69]
	<b>Fagaronine</b>	
3. Quinones		
		[70]
	<b>Isofuranonaphthoquinone</b>	

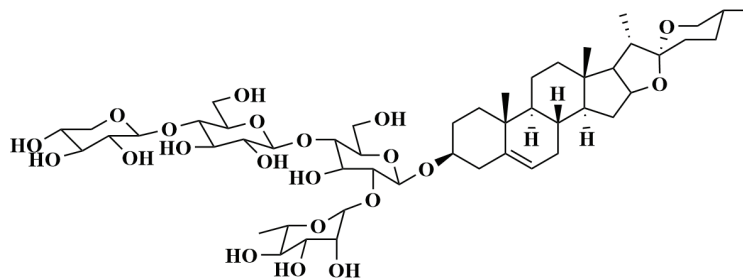
Class of compounds	Structure	References
--------------------	-----------	------------

4. Saponins



[74]

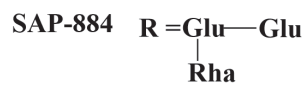
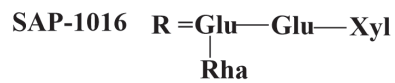
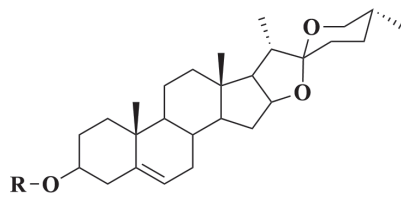
**Balanitin-6**



[74]

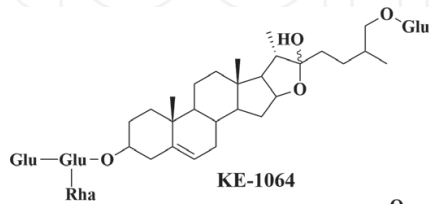
**Balanitin-7**

5. Steroids

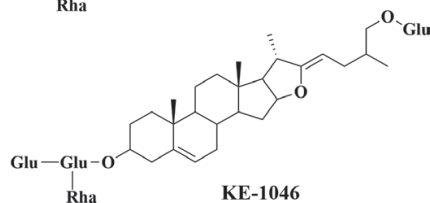


[73]

**Spirostanes**



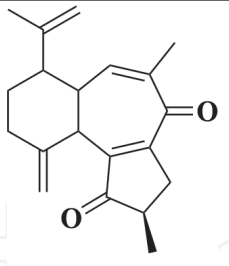
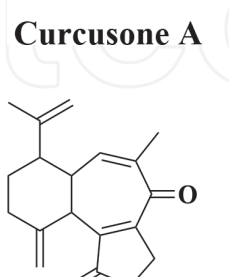
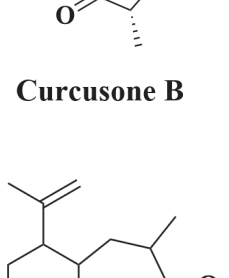
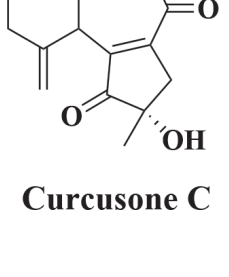
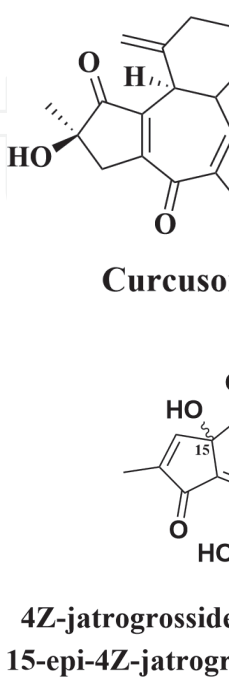
**KE-1064**

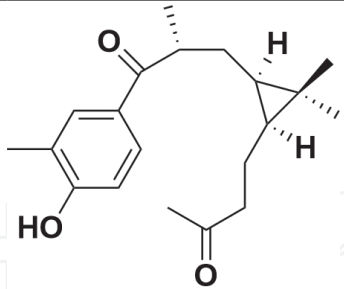
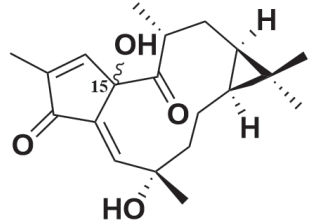
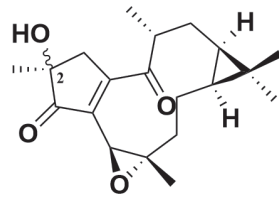
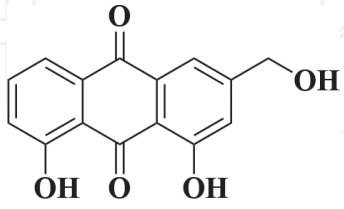


**KE-1046**

[73]

**Furostanes**

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

Class of compounds	Structure	References
	 <p style="text-align: center;"><b>Multidione</b></p>	[75]
	 <p style="text-align: center;"><b>4E-jatrogrossidentadion 15β- OH</b></p>	[75]
	 <p style="text-align: center;"><b>12-epi-hydroxyisojatrogrossidion 2β- OH</b>  <b>2-hydroxyisojatrogrossidion 2α- OH</b></p>	[75]
7. Anthraquinone	 <p style="text-align: center;"><b>Aloe-emodin</b></p>	[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 anthelmintic. 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.

## Author details

Newman Osafo<sup>1\*</sup>, Yaw Duah Boakye<sup>2</sup>, Christian Agyare<sup>2</sup>, Samuel Obeng<sup>3</sup>, Judith Edem Foli<sup>2</sup> and Prince Amankwaah Baffour Minkah<sup>2</sup>

\*Address all correspondence to: nosafo.pharm@knust.edu.gh

1 Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

2 Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

3 Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, Virginia, USA

## References

- [1] Kuipers SE, Farnsworth NR, Fong HMS, Segelman AB. Herbal medicines—A continuing world trend. Presentation at the 1st World Federation of Proprietary Medicine Manufacturers Asia Pacific Regional Meeting; Jakarta. 2010. Unpublished
- [2] Agyare C, Obiri DD, Boakye YD, Osafo N. Analgesic Activities of African Medicinal Plants. In: Medicinal Plant Research in Africa. USA: Elsevier Inc; 2013. pp. 726
- [3] Bindseil KU, Jakupovica J, Wolf D, Lavayre J, Leboul J, van der Pyl D. Pure compound libraries: A new perspective for natural product based drug discovery. *Drug Discovery Today*. 2001;**6**:840-847
- [4] Firn RD, Jones CG. Natural products—A simple model to explain chemical diversity. *Natural Product Reports*. 2003;**20**:382-391
- [5] Vuorela P, Leinonen M, Saikku P, Tammela P, Rauha J-P, Wennberg T, Vuorela H. Natural products in the process of finding new drug candidates. *Current Medicinal Chemistry*. 2004;**11**:1375-1389

- [6] Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. *Journal of Natural Products*. 2007;**70**:461-477
- [7] Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nature Reviews Drug Discovery*. 2005;**4**:206-220
- [8] Lam KS. New aspects of natural products in drug discovery. *Trends in Microbiology*. 2007;**15**:279-289
- [9] Li JW-H, Vederas JC. Drug discovery and natural products: End of an era or an endless frontier? *Science*. 2009;**325**:161-165
- [10] Saklani A, Kutty SK. Plant-derived compounds in clinical trials. *Drug Discovery Today*. 2008;**13**:161-171
- [11] Harvey AL. Natural products in drug discovery. *Drug Discovery Today*. 2009;**13**:894-901
- [12] Butler MS. Natural products to drugs: Natural product-derived compounds in clinical trials. *Natural Product Reports*. 2008;**25**:475-516
- [13] Orwa C. *Parinari curatellifolia* Planch. ex Benth. *Parinari curatellifolia* Planch. ex Benth. Agroforestry database 4.0 [Internet]. 2009. Available from: [www.worldagroforestry.org/treedb/AFTPDFS/Parinari\\_curatellifolia.PDF](http://www.worldagroforestry.org/treedb/AFTPDFS/Parinari_curatellifolia.PDF)
- [14] Zuco V, Supino R, Righetti SC, Cleris L, Marchesi E, Gambacorti-Passerini C, Formelli F. Selective cytotoxicity of betulinic acid on tumor cell lines, but not on normal cells. *Cancer Letters*. 2002;**175**:17-25
- [15] Laszczyk MN. Pentacyclic triterpenes of the lupane, oleanane and ursane group as tools in cancer therapy. *Planta Medica*. 2009;**75**:1549-1560
- [16] Sami A, Tarua Mk, Salmea K, Jari Y-K. Pharmacological properties of the ubiquitous natural product betulin. *European Journal of Pharmaceutical Sciences*. 2006;**29**:1-13
- [17] U.S. National Institutes of Health. Evaluation of 20% Betulinic Acid Ointment for Treatment of Dysplastic Nevi (Moderate to Severe Dysplasia) [Internet]. 2010. Available from: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=494341&version=HealthProfessional&protocolsearchid=3664931> [Accessed: August 2010]
- [18] Halilu ME, October N, Balogun M, Lall N, Abubakar MS. Studies of *in vitro* antioxidant and cytotoxic activities of extracts and isolated compounds from *Parinari curatellifolia* (Chrysobalanaceae). *Journal of Natural Sciences Research*. 2013;**3**(13):149-155
- [19] Pan L, Chai H, Kinghorn AD. The continuing search for antitumor agents from higher plants. *Phytochemistry Letters*. 2010;**3**(1):1-8
- [20] Fagbemi JF, Ugoji, Esther AT, Adelowotan O. Evaluation of the antimicrobial properties of unripe banana (*Musa sapientum* L.), lemon grass (*Cymbopogon citratus* S.) and turmeric (*Curcuma longa* L.) on pathogens. *African Journal of Biotechnology*. 2009;**8**(7):1176-1182

- [21] Bhowmik DC, Kumar KS, Chandira M, Jayakar B. Turmeric: A herbal and traditional medicine. *Archives of Applied Science Research*. 2009;**1**(2):86-108
- [22] Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, Ng CS, Badmaev V, Kurzrock R. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clinical Cancer Research*. 2008;**14**:4491-4499
- [23] Kong K-W, Khoo H-E, Nagendra PK, Ismail A, Tan C-P, Rajab NF. Revealing the power of the natural red pigment lycopene. *Molecules*. 2010;**15**:959-987
- [24] Nahum A, Hirsch K, Danilenko M, Watts CK, Prall OW, Levy J, Sharoni Y. Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27 (Kip1) in the cyclin E-cdk2 complexes. *Oncogene*. 2001;**20**(26): 3428-3436
- [25] Bhuvaneshwari V, Nagini S. Lycopene: A review of its potential as an anticancer agent. *Current Medicinal Chemistry – Anti-Cancer Agents*. 2005;**5**:627-635
- [26] U.S. National Institutes of Health. Lycopene in Treating Patients with Metastatic Prostate Cancer [Internet]. 2009. Available from <http://clinicaltrials.gov/ct2/show/NCT00068731> [Accessed: January 2017]
- [27] Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram, NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Research*.. 2004;**24**:2783-2840
- [28] Bishayee A, Politis T, Darvesh AS. Resveratrol in the chemoprevention and treatment of hepatocellular carcinoma. *Cancer Treatment Reviews*. 2010;**36**:43-53
- [29] Athar M, Back JH, Tang X, Kim KH, Kopelovich L, Bickers DR, Kim AL. Resveratrol: A review of preclinical studies for human cancer prevention. *Toxicology and Applied Pharmacology*. 2007;**224**:274-283
- [30] Fulda S, Debatin K-M. Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol. *Oncogene*. 2004;**23**:6702-6711
- [31] ClinicalTrials.gov. Resveratrol for Patients with Colon Cancer. [Internet]. 2009. Available from: <http://clinicaltrials.gov/ct2/show/NCT00256334>. [Accessed: December 2016]
- [32] Van Quaquebeke E, Simon G, Andre A, Dewelle J, El Yazidi M, Bruyneel F, Tuti J, Nacoulma O, Guissou P, Decaestecker C, Braekman J-C, Kiss R, Darro F. Identification of a novel cardenolide (2"-oxovorucharin) from *Calotropis procera* and the hemisynthesis of novel derivatives displaying potent *in vitro* antitumor activities and high *in vivo* tolerance: structure-activity relationship analyses. *Journal of Medicinal Chemistry*. 2005;**48**:849-856
- [33] United States Department of Agriculture (USDA). *Calotropis procera* (Aiton) W. T. Aiton. Germplasm Resources Information Network. 2001. [Accessed: January 2017]
- [34] Mijatovic T, Lefranc F, Van Quaquebeke E, Van Vynckt F, Darro F, Kiss R. UNBS1450: A new hemi-synthetic cardenolide with promising anti-cancer activity. *Drug Development Research*. 2007;**68**:164-173

- [35] Juncker T, Schumacher M, Dicato M, Diederich M. UNBS1450 from *Calotropis procera* a regulator of signaling pathways involved in proliferation and cell death. *Biochemical Pharmacology*. 2009;**78**:1-10
- [36] Unibioscreen. The pipeline—UNBS 1450 [Internet]. 2009. Available from [http://www.unibioscreen.com/randd/pipeline\\_unbs1450.html](http://www.unibioscreen.com/randd/pipeline_unbs1450.html) [Accessed: August 2010]
- [37] Sharma P, Sharma JD. *In-vitro* schizonticidal screening of *Calotropis procera*. *Fitoterapia*. 2000;**71**:77-79
- [38] Tsopmo A, Awah FM, Kuete V. Lignans and Stilbenes from African Medicinal Plants. *Medicinal Plant Research in Africa*. Elsevier Inc. Jamestown Road, London UK. 2013;435-478pp. <https://doi.org/10.1016/B978-0-12-405927-6.00012-6>
- [39] Lippert JW, III. Vascular disrupting agents. *Bioorganic & Medicinal Chemistry*. 2007;**5**:605-615
- [40] Delmonte A, Sessa C. AVE8062: A new combretastatin derivative vascular disrupting agent. *Expert Opinion on Investigational Drugs*. 2009;**18**:1541-1548
- [41] Belanger JT. Perillyl alcohol: Applications in oncology. *Alternative Medicine Review*. 1998;**3**:448-457
- [42] Barthelman M, Chen W, Gensler HL, Huang C, Dong Z, Tim BG. Inhibitory effects of perillyl alcohol on UVB-induced murine skin cancer and AP-1 transactivation. *Cancer Research*. 1998;**58**:11-716
- [43] Lloria-Prevatt M, Morreale J, Gregus J, Alberts DS, Kaper F, Giaccia A, Powell MB. Effects of perillyl alcohol on melanoma in the TPras mouse model. *Cancer Epidemiology, Biomarkers & Prevention*. 2002;**11**:573-579
- [44] Wiseman DA, Werner SR, Crowell PL. Cell cycle arrest by the isoprenoids perillyl alcohol, geraniol, and farnesol is mediated by p21Cip1 and p27Kip1 in human pancreatic adenocarcinoma cells. *Journal of Pharmacology and Experimental Therapeutics*. 2007;**320**:1163-1170
- [45] da Gama Fischer JdS, Carvalho PC, da Costa Neves-Ferreira AG, da Fonseca CO, Perales J, da Costa Carvalho MdG, Domont GB. Anti-thrombin as a prognostic biomarker candidate for patients with recurrent glioblastoma multiform under treatment with perillyl alcohol. *Journal of Experimental Therapeutics & Oncology*. 2008;**7**:285-290
- [46] Lakdawala AD, Shirole MV, Mandrekar SS, Dohadwalla AN. Immunopharmacological potential of rohitukine: A novel compound isolated from the plant *Dysoxylum binectariferum*. *Asia Pacific Journal of Pharmacology*. 1988;**3**:91-98
- [47] Harmon AD, Weiss U, Silverton JV. The structure of rohitukine, the main alkaloid of *Amoora rohituka* (syn. *Aphanamixis polystachya*) (Meliaceae). *Tetrahedron Letters*. 1979;**20**:721-724
- [48] Bible KC, Kaufmann SH. Flavopiridol: A cytotoxic flavone that induces cell death in noncycling A549 human lung carcinoma cells. *Cancer Research*. 1996;**56**:4856-4861

- [49] Arguello F, Alexander M, Sterry JA, Tudor G, Smith EM, Kalavar NT, Greene JF Jr, Koss W, David MC, Stinson SF, Siford TJ, Gregory AW, Klabansky RL, Sausville EA. Flavopiridol induces apoptosis of normal lymphoid cells, causes immunosuppression, and has potent antitumor activity *in vivo* against human leukemia and lymphoma xenografts. *Blood*. 1998;**91**:2482-2490
- [50] Senderowicz AM. Flavopiridol: The first cyclin-dependent kinase inhibitor in human clinical trials. *Investigational New Drugs*. 1999;**17**:313-320
- [51] Krystof V, Uldrijan S. Cyclin-dependent kinase inhibitors as anticancer drugs. *Current Drug Targets*. 2010;**11**:291-302
- [52] Schwartz GK, Ilson D, Saltz L, O'Reilly E, Tong W, Maslak P, Werner J, Perkins P, Stoltz M, Kelsen D. Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma. *Journal of Clinical Oncology*. 2001;**19**:1985-1992
- [53] Karp JE, Blackford A, Douglas SB, Alino K, Seung AH, Bolanos-Meade J, Greer JM, Carraway HE, Gore SD, Jones RJ, Levis MJ, McDevitt MA, Austin DL, Wright JJ. Clinical activity of sequential flavopiridol, cytosine arabinoside, and mitoxantrone for adults with newly diagnosed, poor-risk acute myelogenous leukemia. *Leukemia Research*. 2010;**34**:877-882
- [54] Kupchan SM, Komoda Y, Court WA, et al. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. *Journal of the American Chemical Society*. 1972;**94**:1354-1356
- [55] Remillard S, Rebhun LI, Howie GA, Kupchan SM. Antimitotic activity of the potent tumor inhibitor maytansine. *Science*. 1975;**189**:1002-1005
- [56] Wolpert-Defilippes MK, Adamson RH, Cysyk RL, Johns DG. Initial studies on the cytotoxic action of maytansine, a novel ansa macrolide. *Biochemical Pharmacology*. 1975;**24**:751-754
- [57] Hamel E. Natural products which interact with tubulin in the vinca domain: maytansine, rhizoxin, phomopsin A, dolastatins 10 and 15 and halichondrin B. *Pharmacology & Therapeutics*. 1992;**55**:31-51
- [58] Rai SS, Wolff J. Localization of the vinblastine-binding site on beta-tubulin. *The Journal of Biological Chemistry*. 1996;**271**:14707-14711
- [59] Kupchan SM, Komoda Y, Branfman AR, Dailey RG Jr. Tumor inhibitors. 96. Novel maytansinoids. Structural interrelationships and requirements for antitumor activity. *Journal of the American Chemical Society*. 1974;**96**:3706-3708
- [60] Ravry MJ, Omura GA, Birch R. Phase II evaluation of maytansine (NSC 153858) in advanced cancer. A Southeastern Cancer Study Group trial. *American Journal of Clinical Oncology*. 1985;**8**:148-150
- [61] Liu Z, Floss HG, Cassady JM, Chan KK. Metabolism studies of the anti-tumor agent maytansine and its analog ansamitocin P-3 using liquid chromatography/tandem mass spectrometry. *Journal of Mass Spectrometry*. 2005;**40**:389-399

- [62] Cassady JM, Chan KK, Floss HG, Leistner E. Recent developments in the maytansinoid antitumor agents. *Chemical and Pharmaceutical Bulletin*. 2004;**52**:1-26
- [63] Deng B. Direct colorimetric method for determination of indigo and indirubin in Qingdai. *Zhong Cao Yao*. 1986;**17**:163-164
- [64] Hoessel R, Leclerc S, Endicott JA, Nobel MEM, Lawrie A, Tunnah P, Leost M, Damiens E, Marie D, Marko D, Niederberger E, Tang W, Eisenbrand G, Meijer L. Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases. *Nature Cell Biology*. 1999;**1**:60-67
- [65] Xiao Z, Hao Y, Liu B, Qian L. Indirubin and meisoindigo in the treatment of chronic myelogenous leukemia in China. *Leukemia & Lymphoma*. 2002;**43**:1763-1768
- [66] Zuo M, Li Y, Wang H, Zhou J, Li H, Liu H, Xin H, Zhang S, Chen X. The antitumor activity of meisoindigo against human colorectal cancer HT-29 cells *in vitro* and *in vivo*. *Journal of Chemotherapy*. 2008;**20**:728-733
- [67] Cooperative Study Group of Phase III Clinical Trial on Meisoindigo (CSGPCTM). Phase II clinical trial on meisoindigo in the treatment of chronic myelogenous leukemia. *Zhonghua Xueyexue Zazhi*. 1997;**18**:69-72
- [68] Fleury F, Sukhanova A, Ianoul A, Devy J, Kudelina I, Duval O, Alix AJ, Jardillier JC, Nabiev I. Molecular determinants of site-specific inhibition of human DNA topoisomerase I by fagaronine and ethoxidine. Relation to DNA binding. *The Journal of Biological Chemistry*. 2000;**275**:3501-3509
- [69] Raina H, Soni G, Jauhari N, Sharma N, Bharadvaja N. Phytochemical importance of medicinal plants as potential sources of anticancer agents. *Turkish Journal of Botany*. 2014;**38**:1027-1035
- [70] Tambama P, Abegaz B, Mukanganyama S. Antiproliferative activity of the isofuranonaphthoquinone isolated from *Bulbine frutescens* against Jurkat T cells. *BioMed Research International*. 2014;1-14 pp. Article ID 752941, 14 pages. DOI: 10.1155/2014/752941
- [71] Behera TJ, Behera S, Bharathi LK. Bitter Gourd: Botany, Horticulture, and Breeding. *Horticultural Reviews*. 2010;**37**:101-141
- [72] Saengsai J, Kongtunjanphuk S, Yoswathana N, Kummalue T, Jiratchariyakul W. Antibacterial and antiproliferative activities of plumericin, an iridoid isolated from *Momordica charantia* vine. *Evidence-Based Complementary and Alternative Medicine*. 2015;**2015**:1-11
- [73] Beit-Yannai E, Ben-Shabat S, Goldschmidt N, Chapagain BP, Liu RH, Wiesman Z. Antiproliferative activity of steroidal saponins from *Balanites aegyptiaca*—An *in vitro* study'. *Phytochemistry Letters*. 2011;**4**(1):43-47
- [74] Gnoula C, Mégalizzi V, De Nève N, Sauvage S, Ribaucour F, Guissou P, Duez P, Dubois J, Ingrassia L, Lefranc F, Kiss R, Mijatovic T. Balanitin-6 and -7: Diosgenyl saponins isolated from *Balanites aegyptiaca* Del. display significant anti-tumor activity *in vitro* and *in vivo*. *International Journal of Oncology*. 2008;**32**(1):5-15

- [75] Aiyelaagbe OO, Hamid AA, Fattorusso E, Taglialatela-Scafati O, Schröder HC, Müller WEG. Cytotoxic activity of crude extracts as well as of pure components from jatropha species, plants used extensively in African traditional medicine. Evidence-Based Complementary and Alternative Medicine. 2011;1-7pp. ArticleID 134954,7 pages. DOI: <http://dx.doi.org/10.1155/2011/134954>
- [76] Okoye TC, Akah PA, Nworu CS, Ezike AC. Kaurenoic acid isolated from the root bark of *Annona senegalensis* induces cytotoxic and antiproliferative effects against PANC-1 and HeLa cells. European Journal of Medicinal Plants. 2014;4(5):579-589
- [77] Yordanova A, Koprinarova M. Is aloe-emodin a novel anticancer drug? Trakia Journal of Sciences. 2014;12(1):92-95
- [78] Pecere T, Gazzola MV, Mucignat C, Parolin C, Vecchia FD, Cavaggioni A, Basso G, Diaspro A, Salvato B, Carli M, Palu G. Aloe-emodin is a new type of anticancer agent with selective activity against neuroectodermal tumors. Cancer Research. 2000;60(11):2800-2804
- [79] Kuo P-L, Lin T-C, Lin C-C. The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathway in human hepatoma cell lines. Life Sciences. 2002;71(16):1879-1892