

Review

Anticancer diterpenes of African natural products: Mechanistic pathways and preclinical developments[☆]

Gabrielle Bangay^{a,b}, Florencia Z. Brauning^a, Andreia Rosatella^a, Ana María Díaz-Lanza^b, Eva María Domínguez-Martín^{a,b}, Bruno Goncalves^c, Ahmed A. Hussein^d, Thomas Efferth^e, Patricia Rijo^{a,c,*}

^a Center for Research in Biosciences & Health Technologies (CBIOS), Universidade Lusófona de Humanidades e Tecnologias, Campo Grande 376, 1749-024 Lisboa, Portugal

^b Universidad de Alcalá de Henares. Facultad de Farmacia, Departamento de Ciencias Biomédicas (Área de Farmacología; Nuevos agentes antitumorales, Acción tóxica sobre células leucémicas). Ctra. Madrid-Barcelona km. 33,600 28805 Alcalá de Henares, Madrid, España

^c Instituto de Investigação do Medicamento (iMed.Ulisboa), Faculdade de Farmácia, Universidade de Lisboa, 1649-003 Lisboa, Portugal

^d Chemistry Department, Cape Peninsula University of Technology, Symphony Rd., Bellville 7535, South Africa

^e Department of Pharmaceutical Biology, Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Mainz, Germany



ARTICLE INFO

Keywords:

African
Natural product
Diterpene
Cancer
Mechanism
in vivo

ABSTRACT

Background: The African continent is home to five biodiversity hotspots, boasting an immense wealth of medicinal flora, fungi and marine life. Diterpenes extracted from such natural products have compelling cytotoxic activities that warrant further exploration for the drug market, particularly in cancer therapy, where mortality rates remain elevated worldwide.

Purpose: To demonstrate the potential of African natural products on the global stage for cancer therapy development and provide an in-depth analysis of the current literature on the activity of cancer cytotoxic diterpenes from African natural sources (to our knowledge, the first of its kind); not only to reveal the most promising candidates for clinical development, but to demonstrate the importance of preserving the threatened ecosystems of Africa.

Abbreviations: 5-FU, 5-fluorouracil; 786–0, renal cancer cell line; A549, adenocarcinomic human alveolar basal epithelial cells; AO/EB, acridine orange/ethidium bromide staining; ABC, ATP-binding cassette; CAM, chorioallantoic membrane; CCRF-CEM, acute lymphoblastic leukaemia cancer cell line; CSC, cancer stem cells; DOX, doxorubicin; DSBs, DNA double-strand breaks; DU145, human prostate cancer cell line; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-related kinase; EBV, Epstein-Barr Virus; FaDu, human pharynx squamous cell line; FAK, focal adhesion kinase; FDA, Food and Drug Administration; GBM, glioblastoma multiforme; GI₅₀, concentration of the agent that inhibits growth by 50%; GO, Gene Ontology; HCC, hepatocellular carcinoma; HCT116, human colorectal carcinoma cell line; HCT8, human ileocecal adenocarcinoma; HEk293, normal embryonic kidney cell line; HeLa, cervical cancer cell line; HepG2, hepatocellular carcinoma cell line; HER2, human epidermal growth factor receptor-2; HFPS, Human farnesyl pyrophosphate synthase; HL-60, human leukaemia cell line; HL-7702, human hepatic cell line; HMVECs, human microvascular endothelial cells; HO-1, heme oxygenase; HSPs, heat shock proteins; HT29, human colorectal adenocarcinoma cell line; IL, interleukin; iNOS, inducible nitric oxide synthase; IC₅₀, concentration needed to inhibit a to half of the maximum; JNK, c-Jun N-terminal kinase; K562, chronic myelogenous leukaemia cell line; Keap1, Kelch-like ECH-associated protein 1; KEGG, Kyoto Encyclopedia of Genes and Genomes; KG1, erythroleukaemia cell line; KYSE-150, oesophageal cancer cells; LC₅₀, amount of a substance suspended in the air required to kill 50% of a test animals; LPS, lipopolysaccharide; M14, melanoma cell line; MCF-7, breast cancer cell line; MDA-MB-231, triple-negative breast cancer cell line; MDR, multidrug resistant (cancer); MIA PaCa-2, human pancreatic cancer cell line; MAPK, mitogen-activated protein kinase; MMP, mitochondrial membrane potential; MMP-9, matrix metalloproteinase-9; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; MDM2, Mouse double minute 2 (oncoprotein); NCI-60, National Cancer Institute 60 different human tumour cell lines; NCI-H1299, human non-small cell lung carcinoma; NCI-H1975, non-small cell lung cancer; NF-κB, nuclear Factor κ B cells; NO, nitric oxide; Nrf2, nuclear factor erythroid-2 related factor-2; OVCAR8, ovarian carcinoma cell line; PBMC, peripheral blood mononuclear cells; P-gp, permeability glycoprotein; PKC, protein kinase C; PPT, podophyllotoxin; Rho123, rhodamine 123; RNF6, ring finger protein 6; ROS, reactive oxygen species; SAR, structure-activity relationship; SMMC-7721, human hepatocellular carcinoma; Spp., species; SRB, sulforhodamine B; T47D, human breast cancer cell line; TNF-α, tumour necrosis factor α; VEGF, vascular endothelial growth factor.

[☆] This work is dedicated to the memory of Professor Benjamin Rodriguez.

* Corresponding author at: CBIOS-Board Director for Research & Innovation, Natural Bioactives Research Domain-Bio.Natural@CBIOS, Escola de Ciências e Tecnologias da Saúde, Centro Universitário de Lisboa, Campo Grande, 376, 1749-024 Lisboa – Portugal.

E-mail address: patricia.rijo@ulusofona.pt (P. Rijo).

<https://doi.org/10.1016/j.phymed.2024.155634>

Received 4 January 2024; Received in revised form 7 March 2024; Accepted 11 April 2024

Available online 16 April 2024

0944-7113/© 2024 Elsevier GmbH. All rights reserved.

Methods: A comprehensive search by means of the PRISMA strategy was conducted using electronic databases, namely Web of Science, PubMed, Google Scholar and ScienceDirect. The search terms employed were 'diterpene & mechanism & cancer' and 'diterpene & clinical & cancer'. The selection process involved assessing titles in English, Portuguese and Spanish, adhering to predefined eligibility criteria. The timeframe for inclusion spanned from 2010 to 2023, resulting in 218 relevant papers. Chemical structures were visualized using ChemDraw 21.0, PubChem was utilized to search for CID numbers.

Results: Despite being one of the richest biodiverse zones in the world, African natural products are proportionally underreported compared to Asian countries or otherwise. The diterpenes andrographolide (*Andrographis paniculata*), forskolin (*Coleus forskohlii*), ent-kauranes from *Isodon* spp., euphorosphane A (*Euphorbia sororia*), cafestol & kahweol (*Coffea* spp.), macrocyclic jolkinol D derivatives (*Euphorbia piscatoria*) and cyathane erinacine A (*Hericium erinaceus*) illustrated the most encouraging data for further cancer therapy exploration and development.

Conclusions: Diterpenes from African natural products have the potential to be economically significant active pharmaceutical and medicinal ingredients, specifically focussed on anticancer therapeutics.

Introduction

Cancer continues to prevail as one of the leading causes of mortality worldwide, resulting in approximately 10 million deaths in 2020 (Ferlay et al., 2020). Despite recent and promising advances in cancer treatment, conventional therapies continue to display severe adverse effects and are often associated with resistance and relapse. As a result, interest in natural products as alternative or complementary treatments for cancer is of utmost importance (Kueete & Efferth, 2015; Mbaveng et al., 2017). Natural products, including plants and fungi, have long been used in traditional folk medicine as they are known to be rich in biologically active compounds that can yield various anticancer effects (Van Wyk, 2020). In recent years, there has been a surge of interest in the study of natural products for cancer treatment and several compounds have shown promising results in preclinical and clinical studies (Ashrafizadeh et al., 2020; Yang and Ping Dou, 2010). These encouraging compounds may provide safer and more effective options for cancer patients, especially if combined with conventional therapies.

Natural products in cancer therapy

Numerous natural products have been exercised as chemotherapy drugs throughout the many decades of cancer research. The most famous examples are the taxenes (paclitaxel, docetaxel) and the Vinca alkaloids (vincristine, vinblastine), derived from *Taxus brevifolia* Nutt. (Pacific yew tree) and *Catharanthus roseus* (L.) G.Don (Madagascar periwinkle), respectively (Ashrafizadeh et al., 2020; Moudi et al., 2013). Yet, these drugs also have significant concerns pertaining to the adverse effects they exhibit. As such, researchers and academics alike are continuing the hunt for novel natural products that promote fewer side effects without mitigating their effectiveness on cancer patients. More recently, curcumin, the principle active component of *Curcuma longa* L. (turmeric), and resveratrol, the key compound in grapes and red wine, triggered apoptosis in cancer cells, with curcumin demonstrating its potential use as adjunctive therapy to paclitaxel (Ashrafizadeh et al., 2020).

Diterpenes are a large class of organic compounds from the terpene family of secondary metabolites that are widely dispersed in nature and possess diverse biological activities, including anticancer properties (Hussein, 2018). These compounds have repeatedly shown their capacity to inhibit tumour growth and induce apoptosis, making them ideal candidates for cancer treatment (Yang and Ping Dou, 2010). Most famously, paclitaxel, better known by its trade name, Taxol®, a naturally occurring diterpene, was originally derived from the bark of *T. brevifolia* and has been used to treat a variety of cancers, including ovarian, breast and lung carcinoma (Domínguez-Martín et al., 2023). It operates by interfering with the normal function of microtubules, which are involved in cell division and is effective in treating both early and advanced stages of cancer. Compounds like paclitaxel showcase the potential of diterpenes in combating cancer and underscore the

importance of further research and development in this area. Given the significance of diterpenes as anticancer drugs, we have chosen to focus on this class of natural products to illustrate the considerable anticancer potential of African plants containing these compounds.

African natural products as a source of medicinal compounds

The African flora, characterized by its rich biodiversity, has been used for centuries in traditional medicine across the continent (Van Wyk, 2020). With 21,250 vascular plants, South Africa alone is the sixth most species-rich country in the world (Dauby et al., 2016; Rhett A. Butler, 2020). Africa has five recognized biodiversity hotspots: Cape Floristic Region (South Africa), Succulent Karoo (South Africa and Namibia), Eastern Afromontane (Ethiopia, Kenya, Tanzania, Uganda, and more), Coastal Forests of Eastern Africa (Somalia to Mozambique) and Guinean Forests of West Africa (Guinea to Nigeria) (Forest et al., 2007; Marshall et al., 2016). The vastness and ecological diversity of Africa offer a myriad of habitats, ranging from lush rainforests to expansive savannas, arid deserts and diverse wetlands, promoting diverse ecosystems that provide a home to an extraordinary array of flora and fauna (Forest et al., 2007). However, despite significant progress in biodiversity research, a substantial portion of African species (spp.), particularly in remote or inaccessible regions, have yet to be thoroughly studied or documented (Bezeng et al., 2017; Gill et al., 2019). These hotspots are vital for conservation due to their high spp. diversity and endemism, facing threats such as habitat loss and climate change (Catarino and Romeiras, 2020; Linder, 2014; Sosef et al., 2017).

The diverse plant spp. found in Africa have been employed for millennia to treat various ailments and maintain overall well-being (Van Wyk, 2020). With a deep understanding of their surroundings, indigenous communities have developed a wealth of knowledge about the medicinal properties of these plants, which are now attracting attention from modern healthcare practitioners and researchers worldwide (Adewole, 2020; Bezeng et al., 2017; Buenz et al., 2018; Moyo et al., 2015; Okaiyeto and Oguntibeju, 2021; Zofou et al., 2013). The use of African flora in healthcare encompasses a wide range of applications, including herbal remedies, dietary supplements and essential oils. Many of these plants contain bioactive compounds with potential therapeutic effects, offering promising opportunities for drug development (Zofou et al., 2013) and alternative treatment options. For example, in Egypt, the leaves of *Coleus forskohlii* were traditionally used as an expectorant, emmenagogue and diuretic (Yashaswini and Vasundhara, 2011). Elsewhere, the plant *Euphorbia peplus* was used as a purgative and for respiratory conditions, such as asthma and bronchitis (Kemboi et al., 2020). In addition, the bark and leaves of the *Warburgia ugandensis* Sprague (African Pepper) tree have been traditionally used in African medicine to treat various ailments and diseases, including cancer. Extracts from *W. ugandensis* possess cytotoxic properties and can inhibit the growth of cancer cells, making it a subject of interest for further exploration (Denis et al., 2018). Additionally, *Sutherlandia frutescens* (L.) W.T.Aiton (Cancer

Bush), indigenous to Southern Africa, is a plant that has been used for centuries to support immune function and overall well-being. It contains compounds such as canavanine, pinitol and L-canavanine, which have shown anticancer potential in preclinical studies (Lin et al., 2016; van Wyk and Albrecht, 2008). These examples highlight only a fraction of the vast medicinal potential found in African flora (Linder, 2014). The traditional knowledge of indigenous communities, combined with modern scientific research, has the potential to unlock further therapeutic applications.

However, it is important to approach the utilisation of African flora ethically and sustainably, ensuring the preservation of both the plant spp. and the cultural heritage associated with their use (Soejarto et al., 2005). In addition, it is of utmost importance to prioritise the sustainable harvesting and conservation of African plant spp. (Kasagana and Karumuri, 2011). Respecting the local communities and their traditional knowledge, while ensuring fair benefit-sharing, are vital aspects of conducting ethical research and responsibly utilising African flora in the context of cancer treatment (Efferth et al., 2019; Heinrich et al., 2018; Efferth et al., 2016; Soejarto et al., 2005). Unfortunately, sub-Saharan ecosystems are anticipated to face significant detrimental consequences from future climate change, as approximately 90% of spp. are projected to experience the loss of some or most of their climatically suitable habitats by the year 2085 (Stévant et al., 2019). In this context, it is evident that no nation in tropical Africa can be considered thoroughly surveyed. This situation can be partly attributed to political factors, limited initiatives focused on collecting flora, and conflicts or social instability in African nations, which have resulted in vast regions lacking comprehensive data (Lindsell et al., 2011). As collecting efforts in tropical areas also declined, there is a pressing need for both expanded botanical collection endeavours and enhanced digitization of tropical African plant collections (Sosef et al., 2017).

Mechanisms of action of diterpenes in cancer treatment

Diterpenes exert their anticancer effects through a wide range of mechanistic pathways. For instance, some diterpenes target enzymes that are involved in DNA synthesis to inhibit tumour cell proliferation, while others activate certain signalling pathways to induce cell cycle arrest (An et al., 2021; Cardoso et al., 2017; Park et al., 2017). In addition, diterpenes are known to block the activity of vascular endothelial growth factor (VEGF), an essential process for tumour growth and metastasis (Peng et al., 2018; Tae et al., 2017).

In highlighting the mechanistic pathways of diterpenes from African plants, we are interested in comparing with those of established anticancer agents to call attention to the importance of under-explored diterpenes as potential anticancer molecules. It is also important to note that considering the complexity of cancer, modern therapeutic strategies focused on the development of new multifunctional drugs, rather than monofunctional ones, represent a more rational approach for the prevention and treatment of the disease. Therefore, emphasizing the diverse mechanistic pathways displayed by selected diterpenes from African plants is important to disclose their therapeutic utility as multifunctional adjuvants in cancer chemotherapy.

In this review, a 3-fold aim was implemented which addressed the following entities: 1) summarise the current research on natural and semi-synthetic diterpenes found in African natural products as novel anticancer candidates; 2) provide the most up-to-date *in vivo* and pre-clinical and/or clinical data for anticancer diterpenoid compounds; 3) explore the different mechanistic pathways of the lead anticancer diterpenoid compounds.

This work showcases a promising class of compounds with potent anticancer activity, their varied mechanisms of action that are diverse and complex and introduces several compounds that have shown promising results in preclinical and clinical studies to be selected for further studies for the potential treatment of cancer. In addition, the information on their anticancer mechanisms is invaluable for

researchers in the field to evaluate possible synergistic interactions between these compounds and the anticancer drugs established in clinic, as a strategy to reduce toxicity and potentiate the outcome of chemotherapeutics.

The following work also highlights the importance of addressing biopiracy and implementing fair benefit-sharing processes as an essential part in utilising African flora and fauna responsibly. To the best of our knowledge, this is the first review on potential anti-cancer diterpenes that focusses solely on compounds found in African natural products.

Method

To conduct the literature search, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy was employed. Online databases were inspected, including PubMed, Web of Science and Scopus, and an in-depth search for full-text articles in these databases was carried out using two sets of key search terms: "diterpene & mechanism & cancer" and "diterpene & clinical & cancer". The initial search identified 1053 articles. All retrieved publications were managed using Mendeley Reference Manager and duplicates ($n = 517$) were ultimately removed. To ensure only relevant articles were included, specific selection criteria were applied during the initial screening; firstly, articles that did not describe diterpenes found in African plants, fungi and marine organisms were discarded (verified using *Plants of the World Online*). Next, only articles that were published in English, Spanish or Portuguese were inspected. Finally, only papers published between the years 2010 and 2023 qualified for the review (several papers older than 2010 regarding general information around biodiversity and the history of cancer therapy were used for additional supporting information). Articles were only eligible if *in vitro* analysis was accompanied with data on the compounds' mechanisms of action and the activity was assessed against cancer cells or models. Articles not eligible ($n = 290$) for inclusion comprised of studies concerning none or only basic *in vitro* analysis with no mechanistic information and not being related to cancer activity. More explicitly, each paper was thoroughly reviewed to identify diterpenes meeting the selection criteria; those featuring *in vitro*, *in vivo*, or clinical trial data, accompanied by mechanistic studies of diterpenes derived from African natural products were selected for inclusion in the appropriate table (plant, fungi, or marine life origin). Detailed information on each diterpene, including its origin and plant part, when available, experimental model (cell line, assay type, animal model), and results (IC_{50} values in μM , tumour weight/volume changes, percentage of cell detach, etc.) and mechanistic pathway(s), was meticulously extracted from the articles. Additionally, any relevant further information from the papers, such as further results and conclusions about the mechanism of action, was included. Once all compounds of a specific diterpene class were compiled into the appropriate table, the main text elaborated on their similarities, differences and implications, offering a comprehensive analysis of their activity and mechanisms, while suggesting potential directions for further research. Promising diterpene compounds from spp. not native to (or not currently reported in) Africa were discussed in the main text, if the genus or related spp. had been reported, with adequate reasons and explanations for their inclusion. Other relevant compounds in articles that did not fully match the selection criteria (*i.e.*, mechanistic studies performed) were only included in the main text as to provide a better understanding about the current data of the specific diterpene class and as to promote further investigation on African natural products. Overall, 218 relevant papers were included in the literature review. Finally, a full-length inspection of the selected articles was conducted independently by the two main authors. Chemical structures were visualized using ChemDraw 21.0, and PubChem was utilized to search for CID numbers. Accepted plant names were verified in The World Flora Online database.

Results & discussion

Anti-cancer activity of diterpenes from plants

Bicyclic diterpenes

Clerodane

Having been used as a traditional medicinal herb in Ayurveda for the treatment of duodenal ulcers and cancer, seeds from *Polyalthia longifolia* (Sonn.) Thwaites were selected to isolate the active clerodane diterpenes and further evaluate their cytotoxic potential against hepatocellular carcinoma (Tatipamula et al., 2022). The *P. longifolia* (Sonn.) Thwaites variety *pendula* (Annonaceae), widely cultivated in Africa (Gbedema et al., 2015), has produced two interesting drug-like bioactive clerodanes: 16-hydroxycleroda-3,13-dien-15,16-olide (1) and 16-oxocleroda-3,13-dien-15-oic acid (2) (Wu et al., 2014). Notably, both these diterpenes have also been afforded from African *Juticia insularis* T. Anderson.

The biological activity of (1) has been of particular interest, and several studies have been carried out confirming its cytotoxicity against several cancer cell lines. This diterpene has demonstrated pro-apoptotic and anti-proliferation (Chen et al., 2018; Liu et al., 2017; Thiyagarajan et al., 2016; Velmurugan et al., 2018; Zheng et al., 2019), anti-migration and anti-invasion (Chen et al., 2018) and anti-inflammatory activities (Wu et al., 2014; Zheng et al., 2019), as well as synergy with at least one conventional chemotherapeutic agent (tamoxifen) (Velmurugan et al., 2018).

Compound (1) seems to target several oncogenic pathways to perform its cytotoxicity (Chen et al., 2018). Cell cycle arrest, intrinsic and extrinsic apoptosis and autophagy have all been reported as possible mechanisms of action, for which the regulation of anti- and pro-apoptotic factors, such as Bax, p21, Bcl-2, p62 and p53, the down-regulation of cyclins and the involvement of the ERK/MEK/Akt/mTOR pathways have been deemed as crucial (Chen et al., 2018; Cheng et al., 2017; Liu et al., 2017; Thiyagarajan et al., 2016; Velmurugan et al., 2018; Zheng et al., 2019). Moreover, regarding the compound's anti-migration and anti-invasion activities, (1) has been demonstrated to downregulate VEGF, MMP2, MMP9, and FAK, amongst others (Chen et al., 2018).

Interestingly, (1) has also been proposed for the treatment of irritable bowel disease, which is a risk factor for colorectal carcinoma tumorigenesis (Zheng et al., 2019). Different groups have studied the compound's ability to downregulate the NF- κ B pathway (Chen et al., 2018; Zheng et al., 2019), which could be why the compound alleviates inflammation. In this context, (1) has been reported to have higher potential than the conventional chemotherapeutic agent 5-fluorouracil (5-FU) (Zheng et al., 2019).

The other clerodane extracted from *P. longifolia*, (2) has demonstrated cytotoxicity against ovarian cancer cells, which was mediated through apoptosis and anti-inflammatory activities (Wu et al., 2014). However, it should be noted that, generally, (1) has better bioactivity than (2), which could be due to (2) having a more rigid structure and primarily targets kinases - of significant relevance, since kinases are crucial for the initiation and proliferation of cancer. In the future, SAR studies of both (1) and (2), extracted from *P. longifolia*, could prove useful to determine the cause for increased bioactivity of (2). This increased bioactivity should also make (2) a good candidate for further mechanistic and *in vivo* studies.

Another interesting clerodane is crispen E (3) from *Tinospora crispa* (L.) Hook. f. & Thomson (Mantaj et al., 2015) from African rainforests and mixed deciduous forests (Ahmad et al., 2016). Compound (3) demonstrated cytotoxicity against a STAT-3 dependent breast cancer cell line through selective inhibition of STAT-3 dimerization (Mantaj et al., 2015). According to molecular modelling experiments, the SH2 domain of STAT3 is targeted by (3). This is interesting because research conducted *in vivo* has demonstrated that STAT-3 remains constantly

active in a wide range of malignancies, spanning from breast, prostate and head and neck tumours, to multiple myelomas and haematological cancers (Mantaj et al., 2015). Therefore, targeting the dimerization of STAT-3 could prove a promising new therapeutic strategy relevant for a variety of cancers.

The naturally occurring clerodane diterpene polyalthic acid (4) is found in copaiba oil from plants of the *Copaifera* genus (Fabaceae family), a natural tree native to tropical regions of Latin America and West Africa (Morelli et al., 2015). Compound (4) is one of the most popular natural medicines in the Amazon (Mizuno et al., 2015). While (4) has been traditionally used to treat parasitic infections, a study by Chibas et al. (2019) has interestingly demonstrated the selective cytostatic effect of (4) against MCF-7 breast cancer cells, rather than a cytotoxic effect. Encapsulating (4) in polymeric furan nanoparticles enhanced its antiproliferative and (selective) genotoxic activity, indicating that (4) incorporated in polymeric nanoparticles holds promise for breast cancer therapy. The use of nanoparticles allows for improved biological activity and potential elimination of toxic solvents in future studies (Chibas et al., 2019), showing that nanoparticle encapsulation could be a promising technique of diterpene drug delivery. Detailed mechanistic and *in vivo* studies are now necessary to confirm the current results and viability of the system, as well as a clear comparison of *in vivo* results between using the pure compound and the encapsulated compound (Fig. 1).

Halimane

From the traditional medicinal plant found in Africa, *Plectranthus ornatus* Codd has produced the cytotoxic halimane diterpene (5) with drug-like properties. This diterpene has demonstrated relevant cytotoxic potency against 4 cancer cell lines, whilst having no effects against the non-neoplastic cell lines, nor against brine shrimp (*in vivo*). Surprisingly, the results of the research group indicated that (5) can induce apoptosis through two different mechanisms depending on the cancer cell line. The group reported that in the MCF-7 breast, FaDu human pharynx squamous and A459 lung cancer cell lines, (5) induced apoptosis through mitochondrial accumulation of reactive oxygen species (ROS), which caused mitochondrial damage, including a reduction in mtDNA copies, and lead to activation of apoptotic pathways without detection of nDNA damage. However, in the CCRF-CEM leukaemia cancer cell line no differences in mtDNA were reported and detected DNA damage was significantly high (Sitarek et al., 2022b, 2022a). This could mean that (5) can induce apoptosis through the intrinsic mitochondrial pathway or through breakdown of replication forks and the formation of DNA double-strand breaks (DSBs) by chemical genotoxins depending on the cell line. Moreover, Sitarek et al. (2022) also found that the leukaemia cancer cell line was more sensitive and, as such, the second mechanism warrants further research and other cell lines that undergo apoptosis through this mechanism could be better targets for (5) therapy. Furthermore, (5) also exhibited anti-inflammatory effects on the normal cell line when exposed to lipopolysaccharide (LPS), which correlated with the modulation of gene expressions for IL-6, IL-8, tumour necrosis factor α (TNF- α) and GM-CSF (Sitarek et al., 2022), showing (5) could be a promising selective anticancer agent.

The results for halimane (5) are promising. SAR studies could prove useful to determine how to increase the bioactivity of the compound and further *in vitro* (testing on additional cancer cell lines) and *in vivo* studies, specifically using mouse models, are a clear next step to confirm the compound's potential as an anticancer agent (Fig. 2).

Labdane

Labdane diterpenes are mainly found in Lamiaceae family in well-known genera, such as *Coleus* and *Salvia*, although they also appear in other families, such as Asteraceae, Cupressaceae or Zingiberaceae (Akaberi et al., 2016; Hao et al., 2017; Ravera et al., 2021). Different mechanisms seem to be involved in the mode of action of these diterpenes, appearing in many cases the activity in tumoural cells through

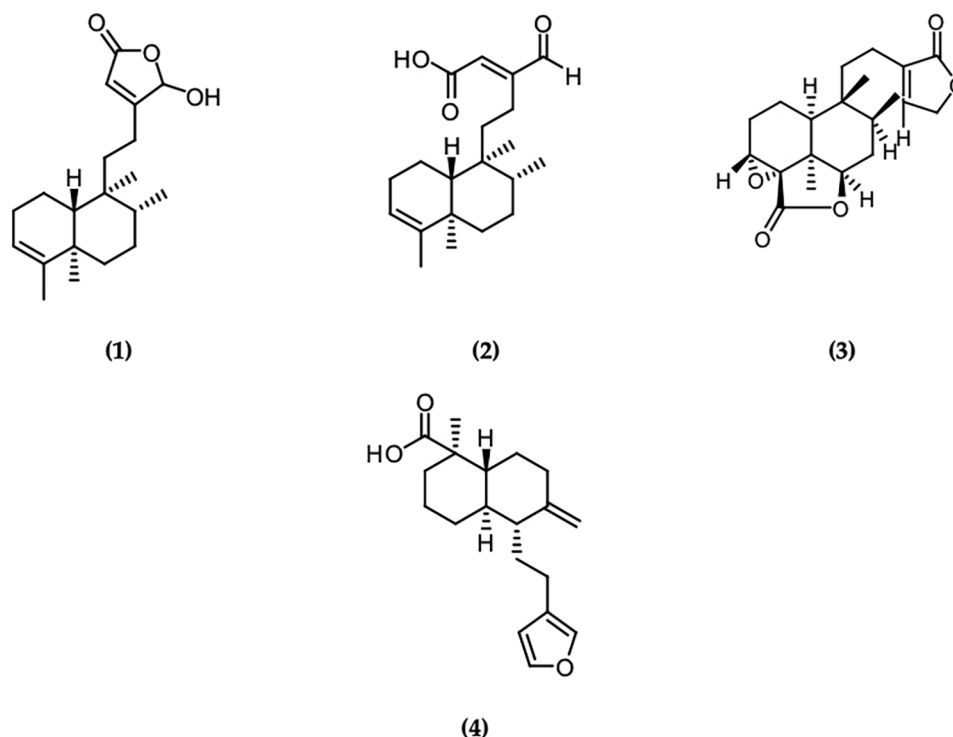


Fig. 1. Chemical structures of clerodane diterpenes 16(α/β)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide (1), 16-oxo-cleroda-3,13(14)E-dien-15-oic acid (2), crispene E (3) and polyalthic acid (4).

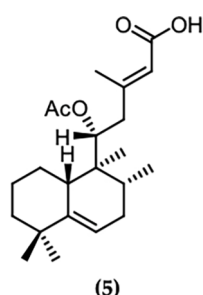


Fig. 2. Chemical structure of halimane diterpene (11R*,13E) -11-acetoxylima5,13-dien-15-oic acid (5).

intrinsic or mitochondrial apoptosis, as well as cyclins level that affect the cell cycle and kinase communication routes, avoiding cell viability and, with them, suppressing tumour growth (Bakhtiari et al., 2021; Balbinot et al., 2019; Franco et al., 2019; Gong et al., 2021; Guo et al., 2018; Liu et al., 2019; Sitarek et al., 2022b, 2022c; Yang et al., 2021; Yue et al., 2020). In addition, there are examples, such as forskolin (6), that not only possess antitumoral properties but also prevent the hearing loss that appeared as an adverse effect of the use of cisplatin (Guo et al., 2018). There has been a clinical trial registered using forskolin-rich *Coleus forskohlii* extract related to cystic fibrosis, yet not with cancer [Clinical Trials Identifier: NCT02143349].

It was also suggested that the labdane diterpene manool (7) could be used as an exogenous antioxidant to avoid the oxidative damage in photoreceptors in pathological conditions, as already demonstrated for other plant-derived antioxidant molecules. Therefore, this compound will be interesting to decrease free radicals and neutralize their harmful effects, preventing healthy cells from being susceptible to becoming cancerous (Ravera et al., 2021).

The cytotoxicity of a labdane diterpene, 1α,6β-diacetoxy-8α,13R*-epoxy-14-labden-11-one (8), against the MCF7 and FaDu cell lines was assessed in MCF7 cells line (IC₅₀ value: 17.49 μg/ml). Similarly, (8)

exhibited cytotoxic activity against the FaDu cell line with IC₅₀ = 32.66 μg/ml. The authors assessed the ROS levels and showed that after 12 h of incubation of MCF7 cells with (8) there was a significant and sustained increase ($p < 0.001$) in ROS levels compared to the control group, which persisted for up to 48 h. Similar results were found for the FaDu cell line; a significant elevation in ROS levels was observed after 12 h of incubation with (8) and this increase was maintained throughout the entire 48 h period. The mitochondrial membrane potential (MMP) was also significantly reduced, and a pointedly higher percentage of apoptotic cell values were observed in MCF7 and FaDu after exposure to (8) when compared to the control. The researchers attributed the apoptotic inductive effects to caspase 3/7 activation. Finally, a preliminary *in vivo* brine shrimp general toxicity assay revealed that the compound showed no toxic effect to the shrimp at 100 μg/ml, after 24 h incubation (Sitarek et al., 2022b). Preliminary *in vivo* results for (8) should be confirmed in other animal models. Moreover, it would be interesting to see further testing of (6), forskolin, as an extract with forskolin is under clinical trial, though for a different ailment. Therefore, it would be interesting to advance our knowledge of this compound, in the hopes that it might reach the clinical trial phase.

The medicinal fern *Aleuritopteris argentea* (S.G. Gmél.) Fée contains the *ent*-labdane alepterolic acid, from which fifteen selective cytotoxic amide derivatives were produced (Zhang et al., 2020). While derivative 1 was the best hit against all cancer cell lines, derivative 11 (9) was the best lead compound with significant toxicity against HeLa cells. Notably, (9) induced apoptosis via a mitochondria-dependent endogenous pathway, with activation of caspase-9 and caspase-3 and subsequent cleavage of poly (ADP-ribose) polymerase. Based on these findings, the 15-carboxyl group of alepterolic acid shows promise for enhancing therapeutic potential through derivatization. The amides from longer chain amines lost potency, while amino moieties such as N, N-dimethylpiperidin-4-amine1 and 4'-bipiperidine hold relevance for optimization. Therefore, the derivatization of natural diterpenes can prove an effective method for improved efficacy. It should also be noted that while *A. argentea* has not been reported in Africa, the genus has and

a recently discovered spp. of *Aleuritopteris* in the African flora suggests the potential for similar compounds (Mingou et al., 2021). Zhang et al. (2020) reported that even within *A. argentea* the content and types of metabolites vary depending on the geographical distribution, which is why the study of *Aleuritopteris* spp. could prove exciting (Zhang et al., 2020). Positive *in vitro* cytotoxicity results of compound (9) should be confirmed *in vivo* and should promote phytochemical surveys to identify possible new *ent*-labdanes in the African spp. *Aleuritopteris farinosa* (Forssk.) Fée (Pteridaceae).

Andrographis paniculata (Burm. f.) Wall. ex Nees has been used for centuries as a traditional herbal remedy across Asia. Moreover, it is also employed in ethnobotanical practices to address ailments such as snake bites, bug bites, diabetes, dysentery, fever, and malaria. Notably, in both Unani and Ayurvedic medicinal traditions, *A. paniculata* is prominently utilized as one of the primary medicinal plants (Hossain et al., 2014). Isolated from *A. paniculata*, andrographolide (10), belonging to the Acanthaceae family, has been gaining momentum as a potential anticancer agent due to its notable potential to interact with different signalling cascades in a variety of cancers (Bassey et al., 2021; Beesetti et al., 2019; Farooqi et al., 2020; Islam et al., 2018; Kandanur et al., 2019; Kumar et al., 2020; Loh et al., 2020; Peng et al., 2018; Yerragunta et al., 2021; Yu et al., 2018; Zeng et al., 2022; Zhang et al., 2022). Concerning the multiple exerted modes of action, the most common ones affect the cell cycle, promoted apoptosis, migration, angiogenesis in tumoral cells and/or affect molecules involved in inflammatory processes (NK-kb, COX-2). Other more specific activities have been described standing out as the senescence promotion, the activity on the H⁺/Na⁺ pumps that regulate the intracellular pH of tumour cells or the synergism exerted with radiotherapy, even in resistant cells (collateral sensitivity) (Beesetti et al., 2019; Loh et al., 2020; Peng et al., 2018; Zhang et al., 2022).

Modifications of (10) at C-3, C-14 and C-19 might lead to desirable bioactive molecules with activity against different tumors as compiled in recent works (Kumar et al., 2020; Zeng et al., 2022). The chemical modifications could change the hydrophilicity of a compound and affect activity and toxicity via its cell permeability. As an example, C14-ester analogues of andrographolide and their α and β diastereomeric epoxy derivatives possessed higher anticancer potency than andrographolide and low toxicity towards normal VERO and MCF-10A cells. Besides, the halogenated (Br/I) related esters of andrographolide were more potent as halogenated compounds exhibiting good anticancer activity (Kumar et al., 2020).

Regarding preclinical toxicity, (10) possessed a high safety profile (although attention should be taken if the dosage of future formulations causes reproductive toxicity and nephrotoxicity) with no pathological changes and could be a good candidate for clinical trials (Kumar et al., 2020; Zeng et al., 2022).

Due to the promising anticancer data of this diterpene, a 2013 randomized Phase 2 clinical study on the treatment of colorectal cancer (AGCRC-013) using (10) with or without Capecitabine was launched [Clinical Trials Identifier: NCT01993472]. However, it was terminated in 2016 due to low accrual rate (NIH, US National Library of Medicine, 2023).

In this context, several formulations of (10) have been proposed (Zeng et al., 2022). One of the most promising in this area would be the inclusion of this compound formulated into nanovesicles of the saponin escin and phosphatidylcholine, to enhance and prolong its anti-hyperalgesia effect and, therefore, improve drug deliverability in patients suffering oxaliplatin chemotherapy-induced neuropathic pain (Vanti et al., 2022).

With its diverse mechanistic pathways and robust findings across multiple studies, lactone (10) holds great promise as a prospective therapeutic agent for the treatment of several cancer types. It seems that the clear direction forward would be to progress towards clinical trials, however, previous efforts in this area proved unsuccessful, due to the low accrual rate. However, a possible solution might be to design a

clinical trial for a different cancer type with more prevalence, such as breast cancer. This could prove fruitful as there are already many positive results regarding breast cancer cell line MDA-MB-231 for (10).

There are many interesting results within the labdane class, which need to be made more robust before the compounds can advance to the clinical trial phase (Fig. 3).

Tricyclic diterpenes

Abietanes

The abietane-type diterpenes, which were first isolated from the genera *Abies* and *Pinus*, are highly represented in the Lamiaceae family (such as *Salvia* and *Plectranthus*) (Phan et al., 2022). Due to the vast worldwide distribution of the spp. that these genera represent, it is not surprising that they are highly studied, such as *Salvia* spp., for which many mechanisms have been studied both *in vivo* and *in vitro* (Akaberi et al., 2015; Hao et al., 2017). It is worth highlighting that several chemical entities in this group of diterpenes induce autophagy, a type of cell death of which there is much to explore. These compounds inhibit the growth of various cancer cells, including breast, pancreatic, prostate, colon and lung cancer (Acquaviva et al., 2022; Phan et al., 2022).

In a recent 2022 publication, the ability of three abietane diterpenoids, coleon-U-quinone (15), 8 α ,9 α -epoxycoleon-U-quinone (16) and coleon U (17) was studied to modulate P-glycoprotein (P-gp), which is known to expel anticancer drugs from multidrug resistant cancer (MDR) cells, leading to reduced drug efficacy. The compounds extracted from *Plectranthus mutabilis* Codd. exhibited notable modulation effects on P-gp; compounds (15) and (16) displayed an increase in rhodamine 123 (Rho 123) accumulation, indicating inhibition of P-gp's efflux activity, if administered at a concentration of 10 μ M. Conversely, compound (17), at the same concentration, reduced the accumulation of Rho123, suggesting its potential to function as a stimulator. Diterpenoids from *P. mutabilis* could be considered as MDR modulators in cancer. New derivatives and their structure–activity studies are important to reinforce abietanes as a new family of P-gp modulators (Ntungwe et al., 2022). Abietanes (15), (16) and (17) showed promise as P-gp modulators. MDR cells have proven an enormous challenge in the treatment of cancer nowadays, which is why all avenues to overcome it should be explored, and further mechanistic, SAR and *in vivo* studies are an important future direction for these compounds.

In another study on dehydroabietinol (18), an abietane diterpene isolated from *Abies spectabilis* (D. Don) Mirb. the authors assessed its potential anti-pancreatic cancer activity against the MIA PaCa-2 cell line and found inhibition of Akt/mTOR signalling pathways and, furthermore, (18) demonstrated the ability to down-regulate important autophagy regulators in a concentration-dependent manner, including Atg5, Atg7, Atg12, LC3-I, and LC3-II, in nutrient deprived medium. In general, diterpenes possessing an aromatic ring C have stronger activity among the isolated constituents [Fig. 4, (15)]. Moreover, diterpenes possessing the C-18 alcoholic group are favoured over ones with carboxylic acid group (5 > 4, 3 > 2). Similarly, methylene is favoured over the ketone group at C-7 (2–6, 7–9) (Phan et al., 2022).

Investigations into the anti-cancer activity of abietanes *in vivo* is limited. Cryptotanshinone (19) from medicinal *Salvia miltiorrhiza* Bunge has been investigated using transcriptomics demonstrating that (19) regulated genes associated with cell cycle, DNA damage, reactive oxygen species (ROS), NF κ B signalling and cellular movement (Wu et al., 2016). (19) induced G2/M cell cycle arrest and intrinsic apoptosis as shown by loss of mitochondrial membrane potential and increased cleavage of caspase-3/7, caspase-9 and poly ADP ribose polymerase (PARP). (19) bound to IKK- β and suppressed the cytosolic migration of p65 to the nucleus. The anti-invasive property of (19) was evident from the inhibition of cellular movement in a fibronectin-based cellular adhesion assay (Wu et al., 2016). It should be noted that while this species is Asian, there is an abundance of African species within this genus that should be studied for their potential anticancer contents (Will and Claßen-Bockhoff, 2014).

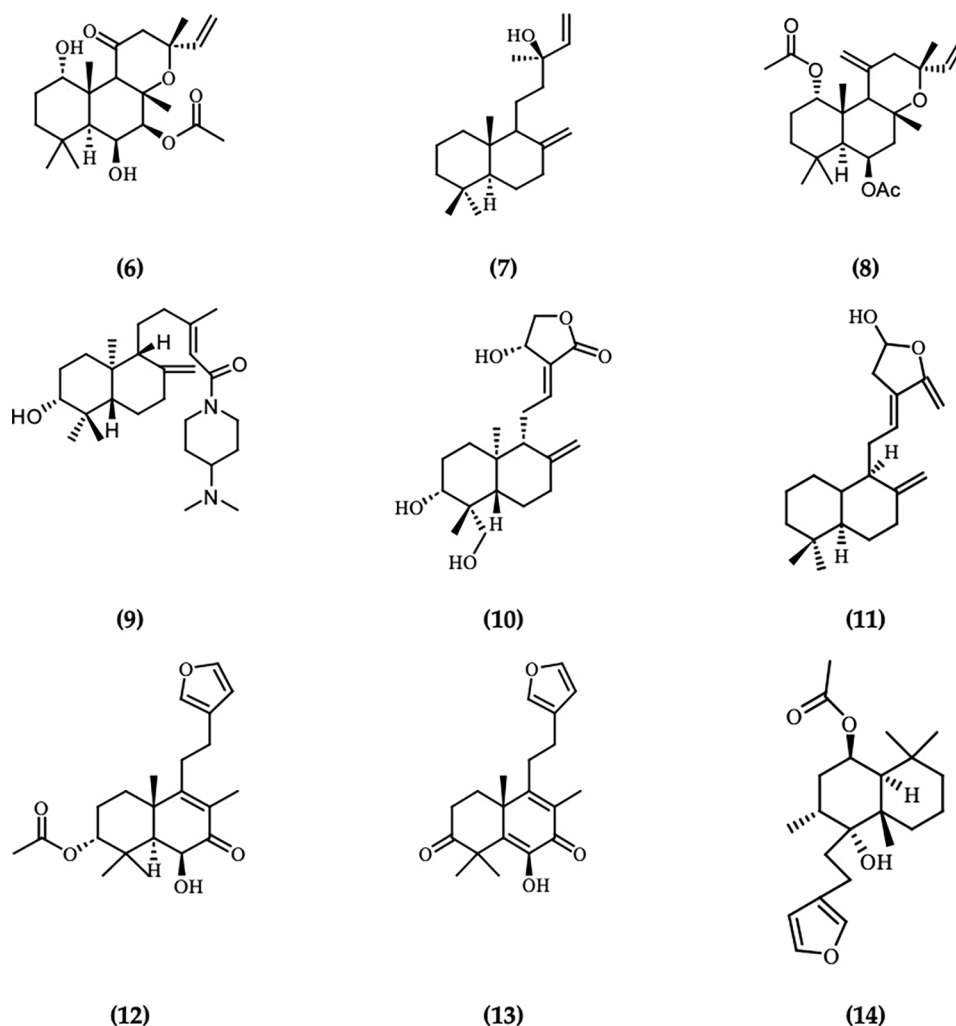


Fig. 3. Chemical structures of labdane diterpenes forskolin (6), manool (7), 1 α ,6 β -diacetoxyl-8 α ,13R^{*}-epoxy-14-labden-11-one (8), alepterolic acid derivative (9), andrographolide (10) coronarin D (11), lejapone B (12), heteronone B (13) and rotundifuran (14).

In a gastric cancer mouse model, (19) significantly inhibited tumour growth rate (76.3%) if compared to the control group (6.7%) and standard treatment with 5-FU (55.4%). Furthermore, combined treatment of (19) and 5-FU resulted in synergistically enhanced tumour growth inhibition (80.9%). The mechanism of action by which this diterpene exerted its activity was identified as the suppression of proteins associated with the JAK2/STAT3 signalling pathway and the reduction of drug resistance-conferring P-gp (Wu et al., 2022).

In an alternative study, a patented abietane-type synthetic derivative (20), that demonstrated the highest *in vitro* anticancer activity in a range of cell lines (MDA-MB-231, MCF-7, T47D, PC3, DU145, HCT116, HT29 and HL60), including potency 25 times higher than the positive control anti-tumour compound podophyllotoxin (PPT) in the T47D cell line, significantly suppressed tumour growth in mice without obvious toxicity. The compound (20) exhibited significant inhibition of tumour volume compared to the control group; after 18 days of treatment, the average tumour volume in the control group was $1220 \pm 127 \text{ mm}^3$ and in the groups treated with 20 mg/kg/day and 40 mg/kg/day of compound (20), the tumour volumes were $654 \pm 129 \text{ mm}^3$ and $401 \pm 143 \text{ mm}^3$, respectively (Wang et al., 2016).

The abietane sugiol (21), which can be found in many *Salvia* spp. and other species, such as *Juniperus formosana* Hayata, *Calocedrus formosana* (Florin) Florin and *Metasequoia glyptostroboides* H.H.Hu & W.C.Cheng, has shown its anticancer capability in various cell lines, including HEC-1-A, HEC-1-B, KLE and PANC-1 ($\text{IC}_{50} = 14, 14, 16 \text{ }\mu\text{M}$ and $\text{EC}_{50}: 9.0 \text{ }\mu\text{M}$,

respectively). Abietane (21) showed its autophagy-mediated anti-proliferative effects, indicated through the increase in the expression of LC3B-II, Beclin-1, Atg5, and Atg12 and decrease in the expression of P62. HEC-1-B cells treated with (21) also demonstrated membrane blebbing and DNA fragmentation. The authors suggest that (21) could exhibit anti-metastatic effects on human cancer cells, since it suppresses the migration and invasion of the of HEC-1-B cells via inhibition of MM-2/9 expressions (Zhao and Zhang, 2021).

Rosemary (*Rosmarinus officinalis* L.) is a well-known herb with a rich historical usage dating back to ancient times. This versatile plant is widely distributed across the globe and has been extensively employed in traditional medicine for various therapeutic purposes. Notably, rosemary was recognized for its abundance of polyphenols, particularly carnosic acid (22) and carnosol (23), which have garnered attention for their remarkable anticancer and antioxidant properties. Considering these beneficial characteristics, several carnosic acid-rich rosemary extracts have been plenty explored regarding their *in vitro* and *in vivo* anticancer effects. Moreover, rosemary extracts standardized to diterpenes [e.g., (22) and (23)] have been granted approval by the European Union (EU) and given a GRAS (Generally Recognized as Safe) status in the United States by the FDA. These regulatory acknowledgments highlight the safety and potential therapeutic value of rosemary extracts. Although rosemary extracts contain a multitude of compounds, the antioxidant and anticancer activity of rosemary extracts has been attributed to its principal components: (22) and (23) (Fernández-Ochoa

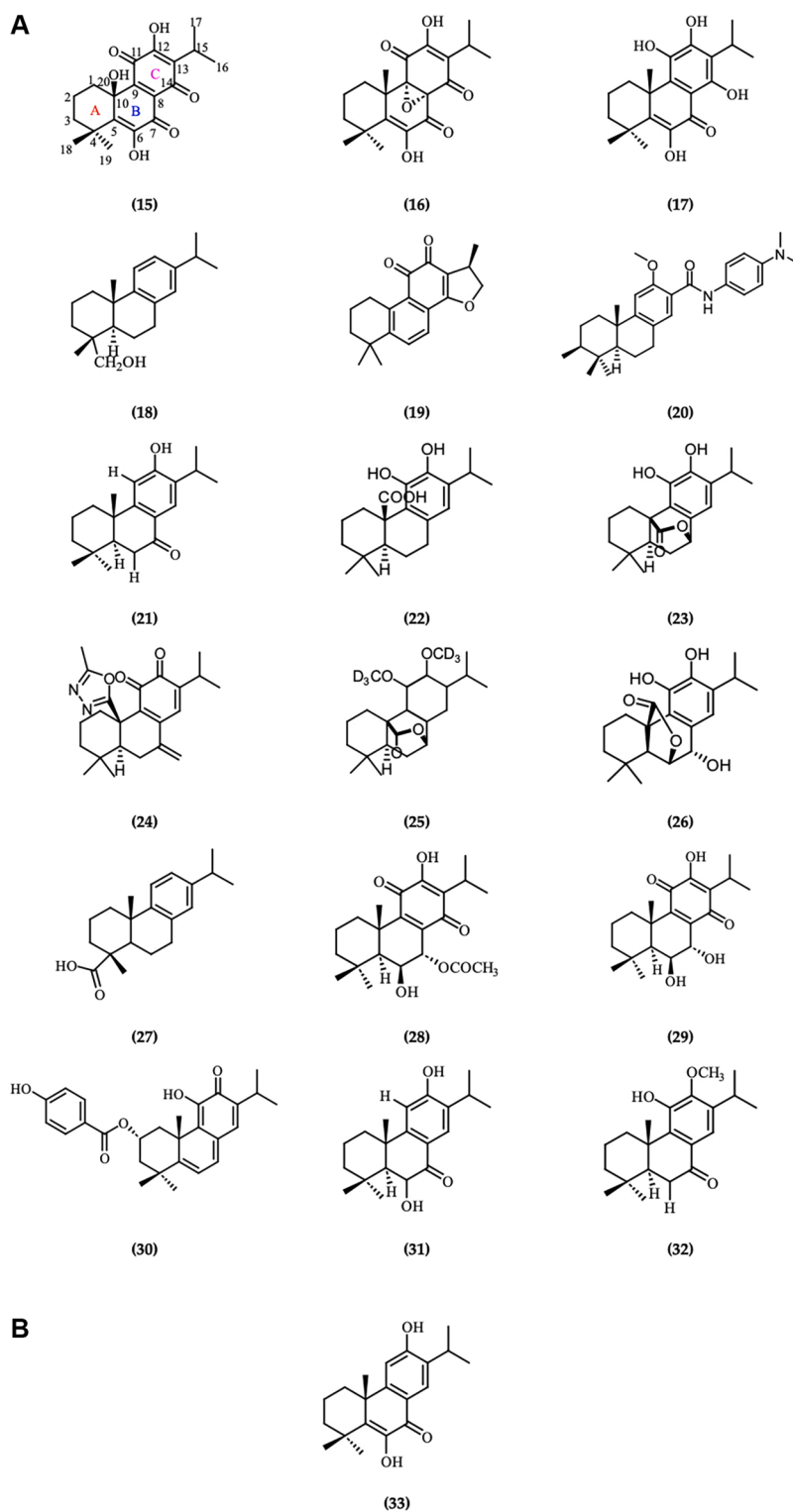


Fig. 4. Chemical structures of abietane diterpenes coleon-U-quinone (15), 8 α ,9 α -epoxycoleon-U-quinone (16), coleon U (17), dehydroabietinol (18), cryptotanshinone (19), patented abietane derivative (20), sugiol (21), carnosic acid (22), carnosol (23), CA28a (24), DCSD (25) and rosmanol (26) dehydroabietic acid (27), 7 α -acetoxy-6 β -hydroxyroyleanone (28), 6 α ,7 β -dihydroxyroyleanone (29), parvifloron D (30), 6 α -hydroxysugiol (31), cryptojaponol (32) and 6-hydroxy-5,6-dehydrosugiol (33).

et al., 2017; Petiwala and Johnson, 2015). The investigation of rosemary extracts, rather than isolated compounds, has gained support due to the synergistic effect observed between (22) and (23) in numerous studies. In that way, (22)-rich extracts, containing (23) as well, were found to display a synergistic antitumor activity both *in vitro* against colon and

pancreatic cancer cells and *in vivo* by inhibiting the growth of colon cancer xenografts in nude mice (González-Vallinas et al., 2014b; Yan et al., 2015). The absence of toxicity towards mice observed for these extracts supported their safe profile, as recognized by the European Food Safety Authority (González-Vallinas et al., 2014b). Preliminary

mechanistic studies have provided insights into the potential signalling pathways mediating the anticancer activity of these extracts in various solid and blood cancers. In colon cancer cells, (22)-rich extracts were found to exert their action via the up-regulation of glycosyltransferase *GCNT3* gene expression, a gene known to possess tumor suppressor properties, and by the down-regulation of its potential epigenetic modulator *miR-15b* gene, thereby offering a non-invasive biomarker to monitor the anticancer effect produced by the extract *in vivo* (González-Vallinas et al., 2014b). Furthermore, they also induced apoptosis and activated Nrf2/sestrin-2 pathway, which mediates antioxidant and inflammation responses (Yan et al., 2015). A supercritical extract of rosemary (SFRE) [12 – 16% composition of phenolic diterpenes (22) and (23)] exerted potent antitumour effects in colon and breast cancer due to its effects on the inhibition of lipid metabolism and DNA synthesis and in the reduction of resistance to 5-fluorouracil in both *in vitro* and preclinical models (González-Vallinas et al., 2015, 2014a, 2013). Additionally, SFRE inhibited non-small cell lung cancer (NSCLC) cell bioenergetics. Several lipid metabolism implicated targets and synergises with standard therapeutic drugs, such as cisplatin, pemetrexed and pembrolizumab were identified (Bouzas et al., 2022). A pilot clinical trial (ClinicalTrials.gov Identifier: NCT03492086) where SFRE was formulated with bioactive lipids (PCT/ES2017/070263) diminished metabolic and inflammatory targets in peripheral blood mononuclear cells (PBMC), such as MAPK, NLRP3 and SREBF1, which may augment the immune antitumor function (De Cedron et al., 2019). These results support the clinical relevance of SFRE as a complement in the treatment of NSCLC patients.

The investigation of rosemary extracts, particularly those rich in (22) and (23), provided a comprehensive approach that harnesses the synergistic effects and potential therapeutic benefits of multiple components. However, extensive research on the effects of the isolated compounds (22) and (23) has also been conducted and shed some light on their remarkable anticancer activity, as well as on the underlying mechanisms that drive their effectiveness. Numerous studies have consistently demonstrated the potent anti-proliferative and cytotoxic properties of (22) both *in vivo* and *in vitro* against various cancer types, including cervical (Su et al., 2016), liver (Gao et al., 2015; Tang et al., 2016), breast (D'Alesio et al., 2017), skin (Lin et al., 2018; Park et al., 2014), pancreas (Han et al., 2019), gastric (El-Huneidi et al., 2021), colon, lung (Liu et al., 2018) and esophagus (Jiang et al., 2021), among others.

In addition, these findings highlighted the multifaceted mechanisms behind (22) anticancer effects. These mechanisms that appear to be cancer type-dependent included apoptosis induction - one of the mechanisms by which (22) exerted its anticancer effects involving the ROS-regulated activation of JNK pathway and endoplasmic reticulum stress, thereby increasing caspase-3 expression. This pro-apoptotic was also observed *in vivo* in nude mice xenograft models of cervical cancer (Su et al., 2016). Nanoparticles of (22) induced apoptosis both *in vitro* and *in vivo* models of liver cancer. This effect was attributed to the regulation of the Akt/Bad signalling pathway (Tang et al., 2016). In gastric cancer cell lines, (22) displayed pro-apoptotic and anti-proliferative activities through the downregulation of survivin and PI3K/Akt/mTOR pathway (El-Huneidi et al., 2021).

Another pathway includes the induction of autophagy: interestingly, in human hepatoma cells, (22) caused the inhibition of the Akt/mTOR pathway which resulted in autophagic cell death (Gao et al., 2015).

Inhibition of cell proliferation and migration was also documented as cancer type-dependent; treatment with (22) resulted in a dose-dependent inhibition of epithelial-mesenchymal transition and migration in B16F10 melanoma cells. This inhibitory effect was achieved through the up regulation of p21 expression, which subsequently induced cell cycle arrest at G0/G1 phase (Lin et al., 2018). In oesophageal cancer cells (KYSE-150), (22) dose-dependently inhibited cell proliferation and colony formation by arresting cell cycle at G2/M phase. Inhibition of metastasis and migration was also observed upon

treatment with (22) most likely mediated by the suppression of ERK, p-38 and JNK signalling pathways (Jiang et al., 2021). It is noteworthy that (22) arrested the cell cycle at different phases depending on the type of cancer, despite achieving the common outcome of inhibiting cell proliferation.

The anti-angiogenic activity of (22) on endothelial cells, was confirmed through an *in vivo* CAM assay, which demonstrated morphological changes in CAM neovascularization, including reduced vascular density and peripheral vessel growth avoidance. These effects were like those observed with other angiogenesis inhibitors and were achieved at comparable or lower concentrations of (22). *In vitro* assays further revealed that (22) inhibited capillary-like tube formation of endothelial BAEC or HUVEC cells in a dose-dependent manner. The inhibition of MMP-2 secretion by (22) suggested its potential involvement in the suppression of extracellular matrix degradation required for angiogenesis (López-Jiménez et al., 2013).

Nanoparticles of (22) have good prevention properties on liver cancer progression by downregulating the Akt/NF-κB signalling pathway and blocking the inflammation response (Tang et al., 2016).

It is also important to mention that hit-to-lead optimization of (22) proved to be an effective strategy in improving its innate anticancer properties. For example, a series of derivatives in the pursuit for new non-bisphosphonate HsFPPS inhibitors. Some of these new derivatives exhibited improved HsFPPS inhibition by >100-fold, if compared with parental molecule, resulting in inhibition of tumor cell growth, down-regulation of Ras prenylation and cell apoptosis in pancreatic cancer cells. Particularly, the quinone derivative CA28a (24) acted as an allosteric non-competitive inhibitor of HsFPPS with slow dissociation kinetics, suggesting potential long-lasting effects *in vivo* (Han et al., 2019).

MDR cell lines expressing ABC transporters (P-gp, BCRP, or ABCB5), oncogenes (mutant EGFR) or the tumour suppressor p53 were not cross-resistant to (22), indicating that (22) is useful to bypass resistance and to inhibit otherwise resistant cells with similar efficacy as drug-sensitive tumour cells (Mahmoud et al., 2020). Furthermore, several studies have provided evidence for the ability of (22) to enhance the efficacy of conventional anticancer treatments. An intriguing synergistic effect was observed when (22) was combined with the monoclonal antibody trastuzumab (Tz), leading to the restoration of the Tz sensitivity in resistant ERBB2+ breast cancer cells (SKBR-3). The underlying mechanism driving this synergistic interaction involved the inhibition of cell survival and migration and cell cycle arrest which were accomplished through ERBB2 downregulation, deregulation of the PI3K/AKT/mTOR signalling pathway and up-regulation of both CDKN1A/p21^{WAF1} and CDKN1B/p27^{KIP1} (D'Alesio et al., 2017). Furthermore, investigations were conducted to explore the combined effect of (22) with alkylating agents, specifically carmustine and lomustine, on melanoma *in vitro* and *in vivo*. The results unveiled that (22) at a dose of 50 mg/kg enhanced the antitumor effects of the alkylating agents. Importantly, (22) supplementation also led to a reduction in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, indicating its favourable safety profile (Lin et al., 2018). The anti-lung cancer effect of intraperitoneally administered cisplatin (1 mg/kg) was boosted by orally administered (22) (10 mg/kg) in Lewis lung cancer bearing mice. Compound (22) inhibited infiltration and function of myeloid-derived suppressor cells and enhanced function of CD8+ cytotoxic T cells, leading to an increased anti-tumour immune-response (Liu et al., 2018).

Carnosol (23) also garnered considerable attention in the realm of cancer research due to its demonstrated effectiveness against various cancer types. Gaining a comprehensive understanding of the specific mechanisms of carnosol that contribute to its anticancer activity is of paramount importance to fully harness its therapeutic potential in clinical settings. Compound (23) has been demonstrated in several studies to inhibit cell proliferation and survival, reduce migration and invasion, and significantly enhance apoptosis of cancer cells. In addition, (23) revealed chemopreventive properties by partially reducing UVB-induced reactive oxygen species (ROS) elevation and thus

protecting DNA from damage in keratinocytes. Furthermore, (23) could inhibit the UVB-induced activation of the pro-survival NF- κ B pathway blocking the skin cancer transformation. The therapeutic effects of carnosol and its analogues dimethyl-carnosol (DCS) (24) and dimethyl-carnosol-D6 (DCSD) (25) were evaluated in the context of cancer cachexia, a complex syndrome associated with muscle atrophy and fat lipolysis that contributes to more than 20 % of cancer-related deaths, in both *in vitro* and *in vivo* experiments. The findings demonstrated that these compounds attenuated the muscle atrophy and fat lipolysis mainly by inhibiting TNF- α /NF- κ B pathway. It is noteworthy that national Chinese patents have been applied for to treat cancer cachexia using (23) (202010089693.1), (24) (202010088733.0), and (25) (202010088747.2) (Lu et al., 2021).

Furthermore, (23) presented synergistic effects if used in combination with other dietary phytochemicals, such as curcumin, towards ovarian (SKOV-3) and breast (MDA-231) cancer cells and potentially inhibited viability of primary cancer cells isolated from the pleural fluid or ascites of patients with metastatic cancers. This synergistic effect may involve the inhibition of different signalling pathways, namely the reduction of Akt and STAT3 phosphorylation. Compound (23) also displayed potent antimetastatic effects in various cancer cells and primary tumour cells by inhibiting the cellular adhesion on fibronectin and the EGF-induced EMT program (which regulates the ability of cancer cells to undergo invasion and metastasis) (Vergara et al., 2014). A cooperative interaction was also observed in glioblastoma multiforme (GBM), the most aggressive form of glioma, cells by increasing the antiproliferative effects of temozolomide (the first-line therapeutic choice for this type of cancer after surgery) (Giacomelli et al., 2017). In the human GBM cell line U87MG expressing wild type p53, (23) at 20 μ M was found to synergize with temozolomide sensitizing glioblastoma cells to chemotherapy. The mechanism that apparently drove this effect involved the inhibition of the MDM2/p53 complex producing a functional reactivation of p53 pathway which elicited apoptosis and cell cycle arrest. Subsequent studies have further elucidated the significance of its effect on p53 pathway in decreasing the human glioblastoma stemness features, thus controlling GBM aggressiveness. Specifically, (23) played a pivotal role in different features of the cancer bulk, namely by decreasing the rate of cancer stem cells (CSC) and promoting the apoptosis of U87MG-derived CSC (cells that possess self-renewal capacity and may be responsible for relapse and metastasis) (Giacomelli et al., 2017). These findings underscored the broader impact of (23), since this compound did not only affect the viability of differentiated GBM cells but also interfered with the diverse processes implicated in cancer resistance and aggressiveness, such as CSC formation, proliferation, and self-renewal.

Another compound that emerged as a promising anticancer agent was the phenolic abietane diterpene rosmanol (26), obtained from various plants, including *Rosmarinus officinalis* L.. This compound inhibited the proliferation of MCF-7 and MDA-MB 231 breast cancer cells (IC₅₀ of 19 and 16 μ M, respectively) while displaying minimal impact on normal human breast MCF-10A cells. Moreover, (26) promoted cell S phase cycle arrest and mitochondrial apoptosis via the inhibition of ERK and STAT3 signals, attributable to the increase in p-p38, the overexpression of protein inhibitor of activated STAT3 and the decrease in PI3K/AKT, ERK and JAK2/STAT3 (Jiang et al., 2021).

Overall, based on our comprehensive literature review, the primary phenolic diterpenes that have emerged as promising contenders in cancer research were derived from rosemary extracts, specifically (22) and (23). Although several studies have demonstrated that both diterpenes scavenged free radicals and interfered in cellular processes such as cell proliferation, they may not necessarily exert the same effects at the molecular level and may differ concerning the cancer type. The multifaceted actions of these compounds encompassed a range of mechanisms, including the induction of apoptosis, inhibition of cell proliferation and migration and the provision of antioxidant and anti-inflammatory effects, positioning them as promising candidates for

further exploration. It is also of great importance the synergistic effects of (22) and (23) combined with other antineoplastic agents in clinical settings. Noteworthy, both (22) and (23) exhibited selective cytotoxicity towards cancer cells in both *in vitro* and *in vivo*, thereby further expanding their therapeutic potential.

Future studies should focus on elucidating the synergistic effects of rosemary extracts containing (22) and (23) with other phytochemicals or conventional anticancer agents, particularly in clinical settings, to harness their full therapeutic potential. Additionally, research should delve deeper into understanding SAR of (22) and (23), and their derivatives. Moreover, exploring the hit-to-lead optimization strategies of (22) and (23), and their derivatives, as well as new delivery systems, could enhance their anticancer properties. Lastly, clinical trials focusing on the use of rosemary extracts rich in (22) and (23), and on the use of individual compounds, and in combination with standard therapeutic drugs, are warranted to validate their efficacy and safety.

Given that several abietanes are reported as autophagy regulators, further studies regarding the mechanism and SAR of these compounds would prove useful. In the abietane class, there is a notable lack of *in vivo* studies for the African species. The positive *in vitro* and *in vivo* results of compound (19), from an Asian *Salvia* spp., should highlight the importance of developing further studies on the African abietanes, particularly *in vivo* studies and confirmation of the mechanistic pathways in these studies. Moreover, the potential of these compounds as MDR reversal agents should be further explored (Fig. 4).

Cassaines

Cassaine diterpenes are tricyclic natural compounds, isolated from several plant species of the genus *Erythrophleum*, that exhibit anti-cancer properties, including inhibiting cancer cell proliferation, inducing apoptosis and preventing the formation of new blood vessels (Ha et al., 2017; Tae et al., 2017; Thi Nguyen et al., 2020). These diterpenes may also be promising in enhancing the effectiveness of currently employed chemotherapy drugs. Many cassaine diterpenes have equally been discovered from plants that belong to the genus *Caesalpinia*, and some of them exert cytotoxic effects against several cancer cell lines and, therefore, were considered as promising anti-tumour agents (Jing et al., 2019). A 2019 study on cassaine diterpenoids depicted that these compounds are the main characteristic constituent of medicinal plants in *Caesalpinia* genus. Indeed, there are around five main types of structures for these compounds, due to their unique structures, namely, tricyclic cassaine diterpenoids with a fused furan ring, butanolide lactone, tricyclic cassaine diterpenoids and norcassaine diterpenoids (Jing et al., 2019).

Several cassaine diterpenes from the seeds of *Caesalpinia minax* Hance, *Caesalpinia sappan* L. and *Caesalpinia crista* Thunb. showed significant or moderate cytotoxicity against DU145, K562, HepG2, MCF7, HCT116, KB, HeLa and HCT8 cell lines (Jing et al., 2019). Moreover, several new cassaine diterpenoids and cassaine diterpenoid amides were isolated from the Asian *Erythrophleum fordii* Oliv. and tested against non-small cell lung cancer cell lines, such as A549, NCI-H1975 and NCI-H129. The cassaine diterpenoid amines exhibited potential cytotoxic activity against these cancer lines with IC₅₀ values between 0.4 and 5.9 μ M in A549, NCI-H1975 and NCI-H1229 cells (Ha et al., 2017). It should be noted that while this plant species, found in China and Vietnam, has not been reported in Africa, several other species of the *Erythrophleum* genus (Fabaceae family) are indeed primarily found in Africa. Interestingly, *E. fordii* has been used in Chinese traditional medicine to promote blood circulation (Son, 2019). These diterpenoids from an Asian species were included in this review because it is possible that other promising anticancer diterpenoids could be potentially isolated from the African species, and these findings should prompt further research on compounds from the African species.

Further investigations into a series of cassaine diterpenoid amides, namely 3 β -acetyl-nor-erythrophlamide (34) and erythrophlesin H (35), isolated also from *E. fordii*, showed cytotoxic activity against human

leukaemia and ovarian cancer cell lines, respectively. Compound (34) exhibited moderate cytotoxicity against HL-60 leukemia cells with an IC_{50} value of $12.0 \pm 1.2 \mu M$. This mono-amide also showed cytotoxicity against KG1 and HeLa cells with IC_{50} values of 18.1 ± 2.7 and $16.5 \pm 2.7 \mu M$, respectively. Compound (35) exhibited significant cytotoxic activity against OVCAR8 ovarian carcinoma cells with an IC_{50} value of $16.7 \pm 1.3 \mu M$. 3AEP did not show cytotoxicity against normal HEK293 embryonic kidney cells (Thi Nguyen et al., 2020).

Furthermore, (34) induced extrinsic apoptosis in cancer cells which was inversely related to the level of Bcl-2 expression in human lung cancer and human lymphoma cells, as well as angiogenesis inhibition on human umbilical vascular endothelial cells (Kim et al., 2020).

Two new cassaine-type diterpenoids, namely erythrofordins D (36) and E (37), sourced from a Cameroonian collection of *Erythrophleum suaveolens* (Guill. & Perr.) Brenan, were isolated and assessed for anti-tumour activity. In the NCI-60 cancer cell line, (36) and (37) were cytotoxic with mean GI_{50} values of 2.45 and 0.71 μM , mean TGI values of 9.77 and 2.29 μM , and mean LC_{50} values of 26.92 and 11.48 μM , respectively. To account for the *in vivo* activity observed by the crude extract, a hollow fibre activity was carried out using erythrofordin-enriched fraction and confirmed that the chemotype was responsible for its *in vivo* activity (Grkovic et al., 2019).

The main active principle in the seeds of *Caesalpinia sappan* L., a cassaine diterpene named phanginin (38), showed moderate cytotoxicity in HL-60 cell line ($IC_{50} = 11.7 \pm 1.6 \mu M$ after 48 h) through activation of caspases-3, leading to apoptotic cell death. More specifically, an increase in proteolytic cleavage of procaspase-3 into its active form and increased caspase-3 activity from 10 to 30 mM, pointing to apoptosis (Tran et al., 2015).

Cassaine diterpenes proved cytotoxic, however, the mechanism for compounds (35), (36) and (37) remains undetermined. Therefore, studies regarding the mechanistic pathways are a necessity. Moreover, for compound (34) with mechanistic studies, the results should be confirmed *in vivo* (Fig. 5).

Dolabrane

Dolabrane diterpenes exhibit promising anticancer activities by

interfering with multiple pathways involved in cancer development and metastasis, including cell proliferation, inducing cell cycle arrest, promoting apoptosis, suppressing angiogenesis and modulating signalling pathways critical for cancer growth and metastasis (Neumann et al., 2015). Dolabrane diterpenes have shown potential in overcoming drug resistance by sensitising resistant cancer cells to chemotherapy. The mangrove species of *Ceriops tagal* C.B.Rob, distributed through Mozambique and other areas of tropical east Africa, contains dolabrane diterpenes, called tagalsins, which have demonstrated that not only do they induce apoptotic cell death via reactive oxygen species (ROS)-mediated DNA damage, but they also activate the DNA-damage sensor kinases ATM and ATR, leading to cell cycle arrest at the S-G2 phase in leukemic cells. In one study, authors also explored the tagalsin dolabrane diterpene (39) activity *in vivo* using immunodeficient mice xenografted with human CEM leukemic T cells. Treatment with (39) resulted in no tumour development in two mice and significantly delayed tumour growth in the remaining mice compared to control groups and led to a significant reduction in tumour weight without significant adverse effects (Neumann et al., 2015).

Tagalsins such as (39) have had excellent results inducing apoptotic cell death in cancer cells with very low IC_{50} values ($\sim 1 \mu M$ (48 h)), which should warrant further mechanistic studies, as well as confirmation of the mechanism of action in new *in vivo* studies. Furthermore, drug-like properties should be determined, to assess this compound's drug candidature for clinical trials (Fig. 6).

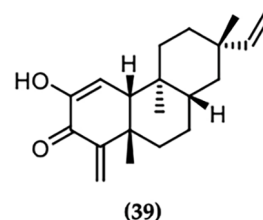


Fig. 6. Chemical structure of dolabrane diterpene tagalsin (39).

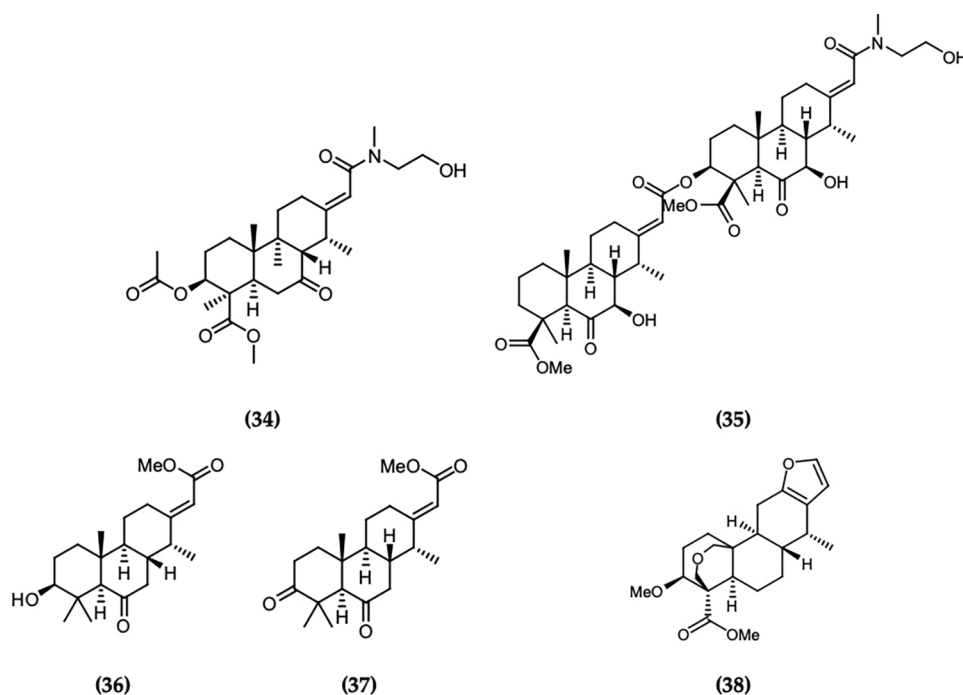


Fig. 5. Chemical structures of cassaine diterpenes 3β-Acetyl-nor-erythrophlamide (34), erythrophlesin H (35), erythrofordin D (36), erythrofordin E (37) and phanginin D (38).

Rhamnofolane

Rhamnofolane diterpenes, are characterized by their rarity in nature and are primarily found in specific plant species from the genera *Rhamnus* and *Croton*. This limited occurrence adds to their uniqueness and intrigue, making them highly valued among researchers.

Having originated from Mexico (McKeon, 2016) but now growing widespread in Tropical areas of Africa, *Jatropha curcas* (Euphorbiaceae family), has been used in traditional medicine to treat ailments in part due to the presence of rhamnofolane diterpenes. In one study, human endometrial cancer cell lines were treated with curcusone C (40), extracted from *J. curcas* roots resulting in reduced cell viability and induced apoptosis in both cell lines through the mitochondrial apoptotic pathway, altering mitochondrial membrane permeability. The release of cytochrome c activated downstream caspases, leading to the cleavage of procaspase-3, procaspase-9, and poly (ADP-ribose) polymerase (PARP). Compound (40) downregulated X-linked inhibitor of apoptosis and survivin. Additionally, it activated the MAPK pathway, including phosphorylation of ERK1/2, JNK and p38, Bim and Bax upregulation, Bcl-xL downregulation, and MAPK pathway activation (An et al., 2021).

There is limited data regarding the efficacy of (40), however, available results are positive. New studies on more cancer lines *in vitro* as well as studies on animal models are necessary (Fig. 7).

Rosane

Thirteen *ent*-rosane diterpenoids with biological activity have been extracted from the aerial parts of *Euphorbia milii* Des Moul. Four compounds, euphominoids A (41), B (42), C (43) and J (44) demonstrated moderate to significant inhibition of Epstein-Barr Virus (EBV) DNA lytic replication (Liu et al., 2017). Liu et al. (2017) also carried out preliminary structure-activity relationship (SAR) studies, indicating that isolated olefinic scaffolds are responsible for the relevant inhibitory activity. These compounds are particularly interesting, because few *ent*-rosane diterpenoids have been extracted so far, and their mechanisms of action could prove interesting and relevant. Moreover, these results are noteworthy in the context of cancer therapy, since EBV can lead to the development of malignancies such as nasopharyngeal carcinoma (which is commonly found in North Africa), Burkitt's lymphoma and Hodgkin's lymphoma. The relevance of diterpenes in the treatment of EBV for cancer prevention relies in the oncogenesis of these tumour cells as well, which include ROS production and activation of the NF- κ B pathways, with EBV contributing to the survival of the cancer cell through apoptosis (Patel et al., 2022). In this review, several diterpenes that target precisely these pathways have been documented, which is why this diterpenes could also prove relevant in the therapy of EBV-related malignancies.

Ent-rosanes (41), (42), (43) and (44) inhibit EBV, which is related to malignancies commonly found in North Africa, such as nasopharyngeal carcinoma. Currently, only *in vitro* results are available, and only for cells with Burkitt lymphoma. Evaluating the cytotoxicity of these compounds against other cancers that arise from EBV or other active similar pathways, as well as detailed studies on the mechanistic pathways targeted by these compounds, would be of interest (Fig. 8).

Tetracyclic diterpenes

Kaurane

Extracted from the Asteraceae family, renowned as being the family for sunflowers and daisies, kauranes are certainly one of the most

promising diterpenes being investigated for anticancer therapy. Concerning these diterpenes, noteworthy studies have been carried on a range of kaurenes, including grandiflorenic acid (45), in several cell lines, in which the antitumoral mechanisms involved are the cell cycle, necrosis, extrinsic and intrinsic apoptosis (Cardoso et al., 2017; Cavalcanti et al., 2009; Costa-Lotufo et al., 2002; Fagundes et al., 2022; Gonçalves et al., 2022; Hueso-Falcón et al., 2010; Lizarte Neto et al., 2013; Rocha et al., 2019).

African species from the Asteraceae family could undergo phytochemical analysis to hopefully identify new kauranes. For (45), it would be adequate to perform more studies to determine the mechanistic pathways targeted in detail, as well as perform *in vivo* studies.

The *Isodon* genus is reported to be a rich source of *ent*-kauranes, which have demonstrated anti-tumour and anti-inflammatory activities (Sarwar et al., 2020; Xu et al., 2018). *Isodon* species are primarily distributed in tropical and subtropical Asia, however, there are at least two species, *Isodon ramosissimus* (Wall. ex Benth.) Murata and *Isodon schimperi* (Vatke) J.K. Morton, in central and southern Africa (Yu et al., 2014). This genus is particularly interesting because it has produced a significant amount of bioactive *ent*-kauranes (Sarwar et al., 2020). Several studies have pointed out that the cytotoxicity of these diterpenoids comes from the α , β -unsaturated carbonyl moiety and the formation of ROS from synthetic derivatives, which also yielded promising results with interesting biological activity, possibly because the lipophilic aromatic groups may cross the cell membrane more readily (Huo et al., 2020; Lin et al., 2015; Sarwar et al., 2020).

Ent-kauranes are known to have anti-inflammatory activity through the inhibition of nitric oxide (NO) production (Sarwar et al., 2020). Interestingly, molecular docking studies conducted by Xing et al. (2020) revealed significant interactions between bioactive *ent*-kauranes (46) and (47) and inducible nitric oxide synthase (iNOS), suggesting a potential mechanism underlying their anti-inflammatory properties (Xing et al., 2020).

Ent-kauranes exhibit cytotoxic activity against various cancer cell lines, including selective activity against NCI 60 cell lines (Isyaka et al., 2020). Notably, Isyaka et al. (2020) obtained several *ent*-kaurene compounds from the leaf extract of *Croton haumanianus* J. Léonard (Euphorbiaceae) that demonstrated 100% cell death for colon (HCT-116) and melanoma (M14) cell lines, and high percentages of cell death (72.92 - 100%) for the renal cells (786-O) (Isyaka et al., 2020). However, toxicity for normal cells was not reported nor were these compounds selected for progression to the five-dose assay.

Regarding the anti-tumor activity of *ent*-kauranes, several mechanisms have been proposed, with ROS production being considered one of the primary ones (Qiu et al., 2017; Sarwar et al., 2020). One group reported the anti-tumour activity of *ent*-kaurane flexicaulin A (48) to be mediated through cell cycle arrest, through a reduction in NF- κ B activation but also an increase in the expression of p21 and p53 (Xia et al., 2019). It is also noteworthy that the synthetic derivatives of (48), with a 4-(chloromethyl) benzoic acid moiety showed enhanced potential as chemotherapeutic agents (Huo et al., 2020). One such derivative, (49) inhibited tumour growth *in vivo* through the mitochondrial pathway, inhibiting tumour growth also through alterations in ROS-related proteins (p-ASK1, p-MKK4, and p-JNK), which suggests the involvement of the ROS pathway in apoptosis promotion as well (Huo et al., 2020). Remarkably, these diterpenes showed very low toxicity against normal cells. This is relevant, because anticancer agents, such as the commonly used paclitaxel, although effective in reducing tumor growth, exhibit undesirable toxicity and a narrow therapeutic index, causing animal deaths even at lower dosages (Huo et al., 2020; Xia et al., 2019). Another *ent*-kauranoid that, like (48), promoted intracellular ROS accumulation, is pteisolic acid G (50). This compound has potential as a therapeutic agent for human colorectal cancer treatment as a novel inhibitor of the Wnt/ β catenin pathway and inducer of apoptosis, warranting further investigation through *in vivo* experiments and comprehensive mechanistic studies (Qiu et al., 2017).

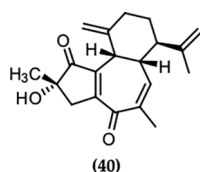


Fig. 7. Chemical structure of rhamnofolane diterpene curcusone C (40).

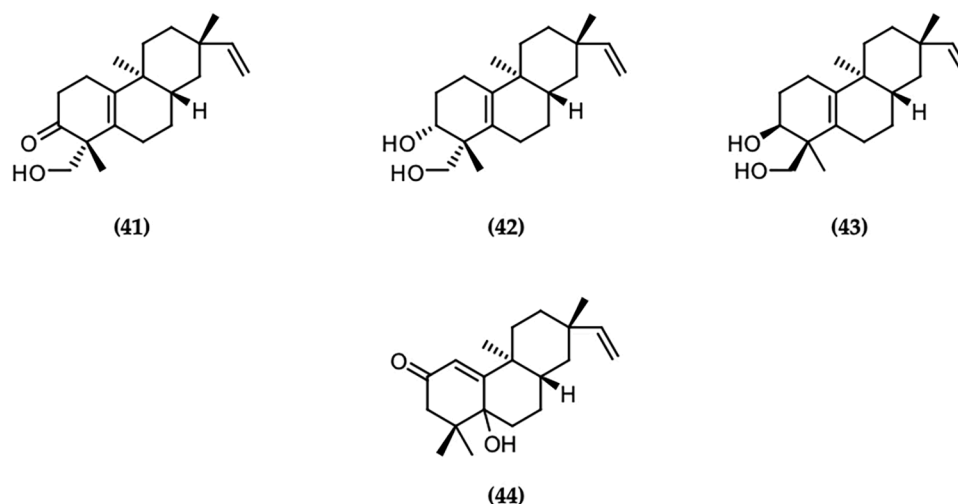


Fig. 8. Chemical structures of rosane diterpenes euphominoids A (41), B (42), C (43) and J (44).

While most studies focused on the tumour inhibition relevance of ROS production, Bodede et al. (2021) reported that several newly discovered cytotoxic *ent*-kauranes exhibited a protective effect against ROS (40% reduction) toxicity on normal cells, which is significant in the context of cancer treatment, given that during cancer the continuous elevation of ROS can infiltrate the immune systems cells and lead to oxidative stress and cell death (Bodede et al., 2021). Interestingly, the research group reports that the significant activity may be due to the presence of two hydroxyl groups.

Other mechanisms of action for *ent*-kauranes have been proposed as well. Liu et al. (2022), reported the post transcriptionally regulation of the expression of oncogenes as a mechanism for the cytotoxicity against aggressive gastric cancer cells of glaucocalyxin A (51). This *ent*-kaurane downregulated MDM2 and RNF6 proteins, which was achieved by restoring miR-3658 levels and inducing SMG1-UPF-mediated mRNA decay of MDM2/RNF6. These findings highlight the dual regulatory mechanisms of (51) involving miR-3658-mediated RNA silencing and SMG1-mediated mRNA decay, both targeting oncogenes, MDM2 and RNF6, and ultimately inhibiting gastric cancer cells (Liu et al., 2022).

Several other *ent*-kauranes have been isolated from the genus *Isodon* with very interesting anti-tumor and anti-inflammatory activities, demonstrating a wide range of mechanisms of action (Sarwar et al., 2020). Sarwar et al. (2020) has published a more detailed review about *ent*-kauranes, including many from the *Isodon* genus. Even though the species containing *ent*-kauranes mentioned in this review are not the ones found in Africa, these examples serve to illustrate the necessity of performing phytochemical surveys on the African species, as they could reveal bioactive *ent*-kauranes. This is especially relevant considering the vast diversity of mechanisms of action of these diterpenes and their promising results *in vivo* against several cancer cell lines with low toxicity.

Moreover, the importance of studying African species is further highlighted by (*ent*-) kaurenoic acid (52), which has been studied by many groups from different plant sources. (52) has been isolated from non-African species *Baccharis retusa* DC. (Silva et al., 2022), *Mikania hirsutissima* (Gardner) Baker (Lizarte Neto et al., 2013) and *Xylopia sericeae* St Hill (Cavalcanti et al., 2009), but also from several African species such as *Copaifera langsdorffii* Desfon (synonym *Copaifera langsdorffii* Desf Kuntze), native to the tropical regions of Latin America and West Africa ISSN Online 1678-4456, *Annona senegalensis* Pers. (Annonaceae) and (Okoye et al., 2012) *Helichrysum rutilans* (L.) D. Don ex G. Don (Popoola et al., 2023). Cytotoxic activity against several cancer cell lines and diverse mechanisms of action, such as the induction of extrinsic apoptosis, necrosis activity, cell cycle regulation and regulation of oncogenes, amongst others, have been reported (Silva et al., 2022)

(Cavalcanti et al., 2009), (Lizarte Neto et al., 2013), (Cardoso et al., 2017) (Costa-Lotufo et al., 2002) (Rocha et al., 2019).

Ent-kauranes are a rich class of diterpenes, many of which have been obtained from Asian *Isodon* spp., with a rich variety of anticancer mechanisms. There are many encouraging results, particularly those from (48) and its derivative (49), which could progress to studies in clinical trials. Current results make it urgent to perform phytochemical surveys on the African species *I. ramosissimus* and *I. schimperii* (Fig. 9).

Phorbol ester

Tiglanol tiglate (53), sold under the brand name Stelfonta®, is a diterpene ester that has garnered significant interest in cancer treatment, in veterinary and, more recently, in humans (Panizza et al., 2019). Derived from the Australian blushwood tree, *Fontainea picosperma* C.T. White, it demonstrates potent anticancer activity by stimulating protein kinase C (PKC) isoforms, particularly PKC- α and PKC- δ , leading to downstream signalling cascades that trigger cell death pathways, including apoptosis, necrosis and autophagy (Barnett et al., 2019). Although not grown directly in Africa, as a member of the Euphorbiaceae family, it is worth pointing out that 47 genera of this family exist in South Africa and with further exploration of African flora, structurally similar diterpene esters may be prevalent and therefore could be pursued for drug development. As of June 2023, (53) is under Phase II clinical trials for the treatment of soft tissue sarcoma [Clinical Trials Identifier: NCT05755113].

(53) is a demonstrated anticancer agent sold commercially and currently in phase II clinical trials for the treatment of soft tissue sarcoma. The compound's source has not been reported in Africa, but 47 species from the same family have and the results for (53) should encourage studies on African natural products (Fig. 10).

Tiglane

In 2020, Tsai et al. (2020), described a prostratin analogue, GRC-2 (54) isolated from *Euphorbia grandicornis*, that presented a 10-fold higher potency than prostratin for inhibiting the growth of NSCLC A549 cells. The cytotoxic effect of these compounds was accompanied by activation and nuclear translocation of PKC- δ and PKD as well as hyperactivation of extracellular signal-related kinase (ERK). The study suggests that prostratin and (54) could be potential anticancer agents for treating non-small cell lung cancer (Tsai et al., 2020) (Fig. 11).

Pentacyclic diterpenes

Kahweol & cafestol

Kahweol (55) and cafestol (56) are natural pentacyclic diterpene alcohols with a kaurane skeleton, extracted from the lipid fraction of the

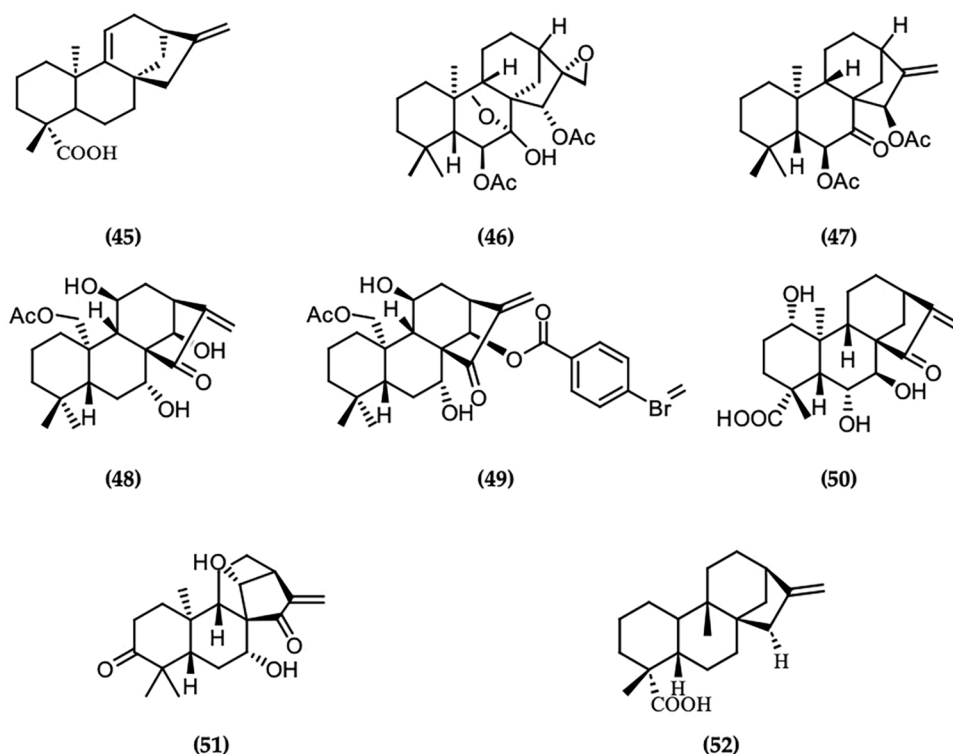


Fig. 9. Chemical structures of kaurane diterpenes grandiflorenic acid (45), isoserrin A (46), isoserrin I (47) flexicaulin A (48), synthetic derivative of flexicaulin A (49), pterisolic acid G (50), glaucocalyxin A (51), and ent-kaurenoic acid (52).

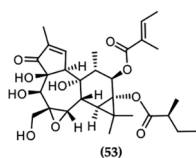


Fig. 10. Chemical structure of phorbol ester diterpene tigilanol tiglate (53).

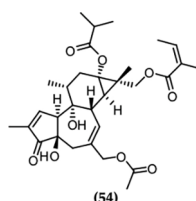


Fig. 11. Chemical structures of tiglane diterpene GRC-2 (54).

coffee beans from *Coffea* spp. During the literature research process, it became evident to give these two kaurene diterpenes their own section in this review, due to the abundance of data and wealth of information about these biologically active metabolites. Even though there are several members of the *Coffea* genus, only *Coffea arabica* L. (Arabica) and *Coffea canephora* Pierre ex. A. Froehner (Robusta) are commercially relevant (Adriana Farah, 2012). These diterpenes can constitute approximately 20% of the lipid fraction of coffee (Farah, 2012), however higher roasting temperatures, longer roasting times and methods of brewing with enhanced filtration can lead to lower levels of the diterpenes (Sridevi et al., 2011). These factors should be kept in mind when considering the biological activities attributed to coffee consumption and the results of clinical surveys. Coffee diterpenes (55) and (56) are reported to present a wide variety of biological activities relevant in the context of cancer therapy, such as anti-proliferative and pro-apoptotic

(Choi et al., 2015; Iwamoto et al., 2019; Lima et al., 2017; Makino et al., 2021; Oh et al., 2018; Park et al., 2017, 2016; Saito et al., 2015; Seo et al., 2018; Tsai et al., 2018), anti-metastatic (Choi et al., 2015; Moeenfarid and Alves, 2020; Seo et al., 2018; Tsai et al., 2018), anti-inflammatory and antioxidant (Seo et al., 2018; Tsai et al., 2018) and anti-angiogenic (Moeenfarid & Alves, 2020; Tsai et al., 2018) activities, as well as modulators of sensitivity to other anticancer agents (Choi et al., 2015; Lima et al., 2017).

A remarkable number of research groups has reported anti-proliferative and pro-apoptotic activities both for (55) and (56), including cytotoxicity against colorectal (Choi et al., 2015; Park et al., 2017, 2016), leukaemia (Lima et al., 2017), breast (Oh et al., 2018), prostate (Iwamoto et al., 2019), renal (Makino et al., 2021) and liver (Seo et al., 2018) cancer cells, amongst others (Silva et al., 2022). The apoptotic effects are due to activation of caspase-3 and/or cleaved PARP (Choi et al., 2015; Iwamoto et al., 2019; Lima et al., 2017; Oh et al., 2018; Seo et al., 2018).

Several research groups have focused on the effects of (55) on colorectal cancer, given the fact that it is a highly prevalent condition with a high rate of mortality. Choi et al. (2015) reported that the expression of heat shock proteins (HSPs), HSP70, was significantly reduced after treatment with kahweol. This is noteworthy because the expression of HSPs is upregulated in many cancer cells, and their overexpression leads to tumor growth and resistance to chemotherapy. Overexpression of HSP70 was also associated with an increase in the phosphorylation of protein kinase B (Akt/PKB). Notably, Choi et al. (2015) also found cell death to be caused by downregulation of anti-apoptotic Bcl-2 and phosphorylation of Akt (Choi et al., 2015). Park et al. (2016) attributed the cytotoxicity of kahweol against colorectal cancer to the proteasomal degradation of phosphorylated cyclin D1 by kahweol-activation of ERK1/2 and JNK or by GSK3b. These results are promising, because cyclin D1 is responsible for uncontrolled cell growth in cancer cells and a reduction of the protein is a known anticancer mechanism (Park et al., 2016). In a second study, Park et al. (2017) further explored the mechanism of action of kahweol against colorectal

cancer. Here kinases ERK1/2 and GSK3 β once again played a crucial role, by upregulating the cis-acting element CREB in the promoter of activating transcription factor 3 (ATF3), a tumor suppressor in colorectal cancer. This eventually led to an increase in cleaved PARP and apoptosis (Park et al., 2017). Therefore, (55) can influence a series of downstream proteins of ERK1/2/JNK/ GSK3 β /Akt and a more comprehensive study that validates the relationship between these reports is necessary.

In fact, the Akt/ERK/JNK pathways are reported many times as crucial to the effectiveness of these diterpenes (Choi et al., 2015; Makino et al., 2021; Oh et al., 2018; Park et al., 2016; Saito et al., 2015; Seo et al., 2018; Tsai et al., 2018). One group, that also reported the inhibition of expression of cyclin D1 to be mediated through the phosphorylation of mTOR and GSK3 β , studied the transcriptional modulation effect of (55) on human epidermal growth factor receptor-2 (HER2) overexpressing cancer cells. HER2 is overexpressed in up to a third of breast cancers and associated to lower survival rates. Notably, the group found that (55) inhibited cell proliferation and induced apoptosis by modulating transcription factors PEA3 and AP2, which regulate the expression of HER2. Moreover, (55) also downregulated promoter activity of the transcriptional regulator of fatty acid synthase (FASN), SREBP-1c. FASN plays a key role in tumorigenesis, by increasing synthesis of fatty acids needed for the cancer cell's survival (Oh et al., 2018).

Remarkably, Seo et al. (2021) shed light on the mechanism behind Akt regulation, which seems to play a central role in the mechanism of (55) and (56), as it is reported in several studies. The group found that expression of the oncogene Src was decreased after treatment with (55). Src is upstream of Akt, which was also inhibited by kahweol in the results of this group. Furthermore, the group also found that Src inhibition led to inhibition of STAT3, which plays a key role in proliferative and anti-apoptotic mechanisms (Seo et al., 2021). Both Iwamoto et al. (2019) and Makino et al. (2021) also reported apoptosis due to lower activation of STAT3 by the coffee diterpenes (Iwamoto et al., 2019; Makino et al., 2021). Finally, cytotoxicity against leukemia cells was mediated through an increase in the mRNA of granzyme B, a cytotoxic effector of natural killer cell KHYG-1. The upregulation could be due to an increase in phosphorylation of granzyme B-related transcription factors ATF-2, c-Jun and CREB. Interestingly, the group suggested that these transcription factors could be regulated by their upstream kinases SAPK/JNK and p38 MAPK (Saito et al., 2015).

Finally, Tsai et al. (2018) reported inhibition of urotensin II by (56) which may play a role in cell proliferation. Importantly, in these studies there are no reports of cytotoxicity by these compounds against normal cells. This means kahweol could present a new multi-tasking anti-cancer therapeutic agent (Tsai et al., 2018).

Metastasis comprises a complex process in cancer progression that involves the movement and attachment of cancer cells from the primary tumor to other tissues, and the inhibition of this process is crucial in cancer therapy (Oh et al., 2018). Kahweol acetate (57), (55) and (56) and a mixture of kahweol acetate and cafestol were reported to regulate key factors for cell invasion in a variety of cancer cells (Iwamoto et al., 2019; Makino et al., 2021; Moeenfarid et al., 2016; Oh et al., 2018; Seo et al., 2021). Several of these studies highlighted the role of Akt inhibition by the coffee diterpenes (Iwamoto et al., 2019; Makino et al., 2021; Moeenfarid et al., 2016; Oh et al., 2018; Seo et al., 2021). According to Choi et al. (2019), kahweol acetate inhibited Akt by phosphorylation as well as p38 MAPK and JNK1/2 and inhibited their downstream target NF- κ B. This decreased transcription and translation of matrix metalloproteinase-9 (MMP-9), which mediated invasion and migration (Choi et al., 2019). Makino et al. (2021) also found that a mixture of cafestol and kahweol acetate, more potent than each compound alone, inactivated Akt as well as ERK, which mediated epithelial-mesenchymal transition (EMT) and migration. Moreover, the group reported in two studies that the mixture inactivated EMT-regulators Snail and Twist, as well as targeted metastasis-proteins

CCR2, CCR5 and CCR6 (Iwamoto et al., 2019; Makino et al., 2021). Seo and colleagues also found that inactivation of Akt by Src inhibition led to downregulation of 4E-binding protein (4E-BP1) and p70S6K translation initiation factor, which promote angiogenesis, cell growth and proliferation (Seo et al., 2021).

These diterpenoids are remarkable in the diversity of pathways they target. As such, (56) also inhibited urotensin II-induced IL-8 expression. Urotensin II and IL-8 may cause, metastasis, angiogenesis and tumour growth (Tsai et al., 2018).

As mentioned, both inflammation and oxidative stress are closely linked to cancer development and progression. Seo et al. (2020) reported the antioxidant properties of (55) to be dependent on ROS elimination by hemoxygenase 1 (HO-1). The increase in HO-1 proteins levels occurred after increased expression of the nuclear factor erythroid-2 related factor 2 (Nrf2). Normally, Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) are bounded. However, if oxidative stress is detected, p62 is activated and binds to Keap1, causing it to dissociate from Nrf2. This activates the cascade that leads to the expression of HO-1. Unexpectedly, (55) did not target p62 (Seo et al., 2020), but achieved increased protein levels of Nrf2 by inhibiting the mRNA translation of Keap1 (Al-Kenany and Al-Shawi, 2023; Seo et al., 2020). (56) can increase nuclear translocation of Nrf2 by activation of ERK, which also results in increased levels of HO-1 (Tsai et al., 2018). Moreover, Al-Kenany & Al-Shawi, (2023) also reported further on the anti-inflammatory properties of cafestol *in vivo*. The diterpene inhibited the NF- κ B pathway, which promotes pro-inflammatory biomarkers IL-1 β and TNF- α , as well as offers several chemoprotective properties. Positively, the diterpene had no toxic effect. In congruence with these results, Lima et al. (2017), also reported that (56) reduced ROS levels in leukemic cells.

As previously mentioned, the JNK and STAT3 pathways were affected by (55) during pro-apoptotic regulation. In this context, Seo et al. (2018) found that an anti-inflammatory effect was achieved by inhibition of these pathways as well, namely of NF- κ B, STAT3, phospho-JNK and phospho-p38 MAPK which inhibited the activation of several inflammatory cytokines (IL-1 α , IL-1 β , IL-6 and TNF- α) (Seo et al., 2018).

The anti-angiogenic properties of coffee diterpenes are reported to be not only due to inhibition of urotensin II-induced IL-8 secretions (Tsai et al., 2018), but also due to, once again, inhibition of the Akt pathway. Its inhibition in turn inhibited the release of pro-angiogenic VEGF on human microvascular endothelial cells (HMVECs). Moreover, the diterpenes also inhibited active VEGFR-2, another key player in angiogenesis of adult endothelial cells. It is noteworthy that these effects were caused by cafestol palmitate (57) and kahweol palmitate (58) (Moeenfarid et al., 2016).

Choi et al. (2015) found that triptolide enhanced kahweol's cytotoxicity by inhibiting HSP70 function. Triptolide is an abietane-type diterpenoid that inhibits HSP70 and has shown anti-tumour effects, including against colon cancer. Several of its derivatives have entered clinical research (Gao et al., 2021). Co-administration of (55) and triptolide could prove a relevant strategy in the treatment of colorectal cancer.

Moreover, Lima et al. (2017) reported that co-administration of (56) and cytarabine, an anticancer drug, resulted in decreased leukaemia cell viability, demonstrating a synergistic effect compared to individual drug treatments (Lima et al., 2017).

Kahweol acetate (59) and cafestol (56) also work in synergy, having more potency when administered together than alone (Iwamoto et al., 2019; Makino et al., 2021). This is relevant because during the normal consumption of coffee, both diterpenes are present. Notably, Makino et al. (2021) suggested that the consumption 3-4 cups of coffee brewed using French press would be necessary to reach the concentration at which the diterpenes had anti-cancer activity. Nonetheless, the consumption of coffee was also associated to higher levels of cholesterol and that the roasting and brewing process affect the diterpenoid content significantly (Silva et al., 2022).

Remarkably, these coffee diterpenes interfered in a series of tumorigenesis pathways, with little or no toxicity against normal cells both *in vitro* and *in vivo*. Therefore, these diterpenes hold enormous potential against a large variety of cancer cells. The Akt pathway seems to play a crucial role in the bioactivity of these compounds and it would be relevant to study how it is mediated in different cancer cells and if it is mediated differently at all. A detailed review about (55) and (56) has been published (Silva et al., 2022).

Extensive research has been conducted on these compounds, with well-established mechanisms across various cancer cell lines. With such exceptional results, it is important to perform studies on animal models to determine the efficacy of each compound alone, co-administered with other coffee compound, or co-administered with other anticancer drugs. Encouragingly, current *in vivo* data suggests a compelling need for these compounds to undergo clinical trials. There are previous reports of coffee used in anticancer clinical trials, however, it is important to study the efficacy of these specific compounds individually. It would also be interesting to include results of the coadministration of these compounds, due to the reports of synergy, and of these compounds with known anticancer agents. Some results indicate that a possible first candidate, pending *in vivo* results, could be colorectal cancer (Fig. 12).

Macrocyclic diterpenes

C₁₉-norditerpenoid alkaloid

One of the most celebrated anti-cancer drugs is a diterpene alkaloid, named paclitaxel, derived from the north-American Pacific yew tree (*T. brevifolia*). This diterpene has been used extensively as a chemotherapeutic drug for the treatment of a range of cancer types (Ashrafi-zadeh et al., 2020). As such, these diterpene alkaloids are a promising class of natural compounds for cancer drug exploration. To date, around 373 diterpenoid alkaloids have been isolated and identified from plants, mostly in the Ranunculaceae family, a family found in Africa, and the cytotoxicity activities of more than 250 diterpenoid alkaloids have been tested. In Africa, these compounds are mainly found in the Euphorbiaceae family and *Aconitum* genus (Qasem et al., 2021). However, the present research in this field is limited; additional research is required before these compounds can be applied as anti-tumour drugs.

Aconitine (61), isolated from *Aconitum* spp., has documented information regarding metabolism *in vivo* in animals and humans and related to its use in Traditional Chinese medicine. (Liang et al., 2018; Qasem et al., 2021; Shen et al., 2020; Thawabteh et al., 2021). Having been used in traditional medicine for centuries, particularly in Asia, this compound has demonstrated its ability inhibit cancer cell growth, induce cell death and suppress tumour growth in preclinical and *in vivo*

studies (Kiss et al., 2017). (61) showed to be a potent apoptotic agent against pancreatic cancer (MIA PaCa-2, PANC-1), breast cancer (MDA-MB-231) and melanoma (B16 cell line). In fact, from the compounds studied by the authors, the most toxic compound (according to LD₅₀) was (61) (Kiss et al., 2017). However, (61) is highly cardio- and neurotoxic due to its interaction with voltage-sensitive sodium channels (Chung et al., 2021).

Due to (61) being highly cardio- and neurotoxic as it interacts with voltage-sensitive sodium channels, SAR studies could serve to identify the characteristics responsible for this interaction, and studies on new delivery systems could also serve to overcome this issue (Fig. 13).

Cembrane

Originally native to the Caribbean, *Nicotiana tabacum* L., commonly known as the tobacco plant, was introduced to Africa in the early 17th century ("The Atlantic slave trade," 2011). Since then, it has become economically cultivated on a global scale. *N. tabacum* contains cembrane-type diterpenes that have been investigated for their cytotoxic effects on various cell lines, including HepG2, SMMC-7721 and HL-7702. One such study utilised several assays, including MTT, Hoechst 33258, AO/EB staining, annexin V-FITC/PI and the Cell RNA Kit to assess the cytotoxicity of α -2,7,11-cyprotermine-4,6-diol (62), a specific cembranoid, and elucidate its mechanism of action. Compound (62) significantly inhibited all three cell types in a time and concentration-dependent manner. However, the inhibitory effect was comparatively weaker on HL-7702 cells than on HepG2 and SMMC-7721 cells. Furthermore, HepG2 and SMMC-7721 cells treated with 20 mg/L of (62) for 24, 48, and 72 h decreased the colony formation ability, suggesting that (62) reduced the ability of hepatocellular carcinoma cells inhibiting colony-forming-related proliferation. Morphological changes were observed in the (62) treated group, with a gradual decline in cell density and cell shrinkage over time. The intercellular space was

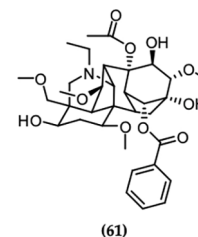


Fig. 13. Chemical structure of *C₁₉*-norditerpenoid alkaloid diterpene aconitine (61).

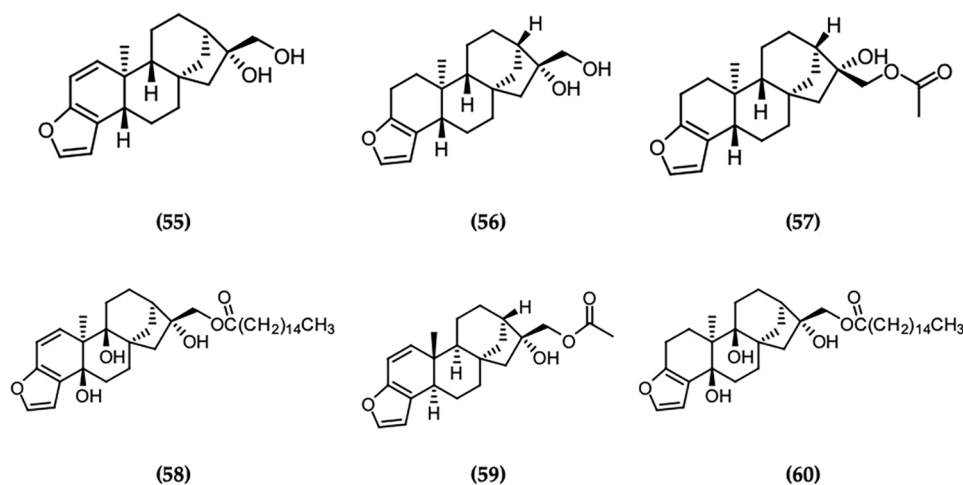


Fig. 12. Chemical structures of kahweol and cafestol-type diterpenes kahweol (55), cafestol (56), cafestol acetate (57), kahweol palmitate (58), kahweol acetate (59) and cafestol palmitate (60).

also expanded. Additionally, AO/EB fluorescence double staining of SMMC-7721 cells revealed similar changes. In HepG2 cells treated with (62), the number of cells in the S phase of the cell cycle increased significantly, indicating an inhibition of hepatocarcinoma cell proliferation. Furthermore, the apoptosis rate of HepG2 cells increased with the duration of (62) treatment, suggesting that (62) induced apoptosis. To understand the underlying molecular mechanisms, expression analysis and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis revealed that the down-regulated genes were associated with cell attachment, cell migration, mitosis, cell cycle, DNA replication and growth factor binding, which collectively inhibited cell survival and proliferation. On the other hand, the up-regulated genes were involved in processes such as protein localisation, metal ion transition, cell death, apoptosis progression, ubiquitin transferase activity and protein transport, which could promote apoptosis. Moreover, the KEGG pathway analysis revealed that the up-regulated pathways were related to NF- κ B signalling, HIF-1 signalling, apoptosis, cancer and autophagy. In contrast, the down-regulated pathways included adhesion, citric acid cycle, conduction pathway, mitogen-activated protein kinase (MAPK) signalling, TGF- β signalling, P13K-Akt signalling and cell cycle. Notably, apoptosis was induced by p53-PUMA, PI3K-Akt and interleukin (IL)-1-NF κ -IAP pathways (Yuan et al., 2019).

Although commonly associated with negative health effects due to smoking, tobacco plants could be repurposed for medicinal use in cancer therapy. This approach not only offers a cost-effective and scalable production system but also offers an opportunity to continue their cultivation. This example also highlights the potential for turning a once harmful plant into a valuable asset to fight cancer.

Interesting *in vitro* results for compound (62) by Yuan et al. (2019), position this compound as a good candidate for *in vivo* studies. Favourable results hold potential for repurposing the source of this compound, *Nicotiana tabacum* L., traditionally associated with tobacco production, into a prospective agent for anticancer therapy (Fig. 14).

Daphnane

Various daphnane diterpenes have shown *in vitro* and *in vivo* activity against different types of cancer, although there are no clinical trials performed with these diterpenes mentioned in Table 1 (NIH, US National Library of Medicine, 2023). Gnidilatin (63) from *Thymelaea hirsuta* Endl. showed a decrease in tumor colonization in male C57BL/6 J mice (Villareal et al., 2018) and Genkwadaphnin (64) from *Daphne genkwa* Siebold & Zuccarini inhibited growth and metastasis both *in vitro* and *in vivo* in BALB/c nude mice with Hep3B xenografts. (64) suppressed DHCR24 expression and activity, as well as DHCR24-mediated cholesterol biosynthesis and lipid rafts formation, then further inhibited hepatocellular carcinoma (HCC) cell invasion and migration (Wu et al., 2020). In addition, many of the compounds isolated in the daphnane class, including (64) come from traditional Chinese medicine natural products and as such are not well documented from African flora. However, given that at least two species from the genus *Daphne* with proven anticancer activities are distributed in North Africa, novel anticancer daphnanes could be potentially found in these African species and the interesting results from compound (64) should serve as an incentive to further study the compounds present in the African species (Moshiashvili et al., 2020).

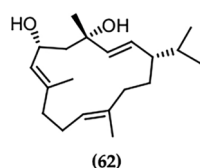


Fig. 14. Chemical structure of cembrane diterpene α -2,7,11-cyprotermine-4,6-diol (62).

Positive results for Asian compounds, including (64) from *D. genkwa*, indicate that it is necessary to carry out more studies on the African species *D. linearifolia*, *D. oleoide*, and *D. gnidium*, which have been used in traditional medicine (Moshiashvili et al., 2020) (Fig. 15).

Ingenane

Commonly found in the *Euphorbia* family, ingenane diterpenes have revealed their aptitude to target various cellular signalling pathways involved in cancer progression and to induce cell death by a variety of mechanisms, including apoptosis (Alves et al., 2022). One ingenane diterpene (ingenol mebutate) (67), isolated from the sap of the petty surge, *Euphorbia peplus*, was marketed as a cancer drug called picato, and had demonstrated activity against melanoma and non-melanoma skin cancer in preclinical studies. Compound (67) acts as a modulator for eight PKC isoenzymes, known to function as either oncogenes or tumour suppressors. These isoenzymes play crucial roles in various physiological processes, including cell proliferation, invasion, angiogenesis, apoptosis, autophagy, differentiation, and senescence, by participating in diverse signalling pathways (Gupta and Paquet, 2013). One phase II clinical trial evaluated the use of (67) in patients with actinic keratosis, a pre-cancerous skin condition, in which the patients treated with (67) reported a high rate of complete response and was eventually approved by the FDA for the treatment of this condition (Peterson and Luke, 2021). However, quite dramatically, the former FDA-approved topical treatment gel, picato, was subsequently suspended by the European Medicines Agency (EMA) when a possible link between patients with actinic keratosis using picato and the development of skin cancer was identified (European Medicines Agency, 2020).

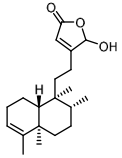
Back in 2006, (67) also entered phase II clinical trial treating early-stage squamous cell carcinoma in which the results showed the 0.05% gel applied to the affected region was well tolerated and the patient remained free of clinical recurrence for the 18 month follow up period (NCT00329121, clinicaltrials.gov). Finally, a review has also been published that compiles different off-label clinical uses of ingenol mebutate (67) topical gel. Treatment of superficial basal cell carcinoma has the greatest evidential support, and hopefully more studies will be forthcoming. The potential of (67) for treatment of squamous cell carcinoma *in situ* and actinic cheilitis are important considerations to keep in mind, especially in cases where other therapies may not have been effective or are not deemed to be viable (i.e.; elderly). In relation to its topical effectiveness, it has been seen that this can increase when, after administration of the (67) gel, the area is occluded with an aluminium disc. Regarding the reported adverse effects, several studies have shown that they can be local and relatively mild, including erythema, itching and inflammation in a lesser extent compared to use of topical 5-FU and topical imiquimod for the same purposes (Del Rosso, 2016).

Given the issues around (67)'s safety profile and serious adverse effects, more robust pre-clinical studies must be carried out before future clinical trials can be considered. It would be interesting to perform SAR studies in the context of cancer treatment, and to also study other ingenanes from *E. peplus* for their anticancer potential.

Lingenol, isolated from the root of *Euphorbia kansu* and traditionally used in Asia for the treatment of edema and asthma, also has tumour inhibition properties. However, its high hepatotoxicity constrains its clinical application (Yan et al., 2016). The understanding of the hepatocyte cytotoxicity molecular mechanism can provide guidance that ensures the safe and effective use of this herb in clinical settings. For that, 3EZ, 20Ac-ingenol (68) inhibited L-O2 cells proliferation and induced cell cycle arrest and apoptosis. Furthermore, the molecular mechanism showed that (68) can enhance the levels of ROS in L-O2 cells and down-regulate the Bcl-2/Bax ratio. These studies provided a systematic approach to assess the safety and effectiveness of this type of compound (Yan et al., 2016). This specific species remains uncharacterized within the African continent; however, numerous taxa belonging to the same genus are distributed in Africa. Its incorporation within this review aims to stimulate additional research into the African taxa, with

Table 1

Anti-cancer activity of diterpenes from **plants** (and their semi-synthetic analogues), their mechanism(s) of action and, where relevant, associated preclinical and clinical data (de Oliveira et al., 2016).

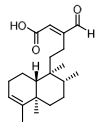
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
BICYCLIC	16(α/β)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide (1) 	<i>Polyalthia longifolia</i> var. <i>pendula</i> (fruits, bark, leaves)	<i>In vitro</i> (MTT and LDH assay, Griess reaction)	N18	IC ₅₀ = 6 ± 0.03 μM (24 h)	↑ nitrite production → autophagy: ↑ ROS accumulation ↓ Antioxidant pool (GSH, SOD, GST, GPx) ↑ LC3-II and Beclin-1 ↑ p-p28 and p-ERK (N18)	↑ nitrite production in N18 and C6 cell line in a dose dependent manner. More potent for C6.	(Thiyagarajan et al., 2016)
				C6	IC ₅₀ = 6 ± 0.03 μM (24 h)			
			<i>In vitro</i> (MTT assay and Flow cytometry)	OECM1	IC ₅₀ = 17.79 μM (24 h)	Autophagy via cell cycle arrest: ↑ G ₀ /G ₁ phase (OECM1) ↓ mTOR (OECM1) ↓ p13K-class III, Akt, Beclin-1 and cyclin D1 ↑ AMPKα, p62, LC3-I and LC3-II	↓ Cell viability in a dose dependent manner.	(Cheng et al., 2017)
				SAS	IC ₅₀ = 14.79 μM (24 h)			
			<i>In vivo</i> (BALB/c nu/nu male mice injected with SAS)		↓ Tumour sizes rate (2 weeks): HCD _{2.0} mg/kg = 24.8 % HCD _{6.5} mg/kg = 55.4 % HCD _{19.5} mg/kg = 66.9 %		HCD: 2.0, 6.5, and 19.5 mg/kg bodyweight. Treated group had a smaller tumour weight and volume. Cell arrangement of control group was denser.	

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (MTT assay, AO/EB dual staining, flow cytometry)	786-O	0, 10, 20, 30, 40 μM CD for 24, 48, and 72 h. ↓ cell viability in concentration- and time-dependent manners. 786-O was more sensitive.	ROS → mitochondrial-dependent Apoptosis: ↑ ROS ↓ MMP ↑ cytosolic cytochrome C ↑ caspase 3 and PARP ↓ Bcl-2, HSP70, pAkt, mTOR, MEK, ERK/2.		(C. Liu et al., 2017)
				A-498				
			<i>In vitro</i> (Clonogenic assay, cell cycle analysis, wound healing, and Transwell assay)	786-O	↓ Colony formation, cell proliferation, migration, and invasion (24h)	Apoptosis: Arrest at G ₂ /M ↑ subG ₁ phase ↓ CDK1, CDK2, CDK4, cyclin B1, cyclin D1, and cyclin E1 ↑ Rounding and substratum detachment. ↓ p21 ↑ p53 ↓ pFAK, FAK, paxillin, vinculin, pSrc, vimentin, pNF-Kb, MMP2, MMP9 and VEGF.	Alterations in a concentration-dependent manner.	(Chen et al., 2018)
				A-498				
			<i>In vivo</i> (IBD induced C57BL/6 male mice)		↓ or no infiltration of lamina propria layer. ↓ IBD symptoms.			(Zheng et al., 2019)
			<i>In vitro</i> (MTT assay)	Caco-2	IC ₅₀ = 4.10 μM (36 h) IC ₅₀ = 2.32 μM (48 h)	Extrinsic and Intrinsic Apoptosis:	↓ cell viability (dose-dependent)	

(continued on next page)

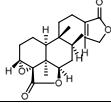
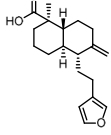
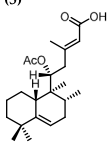
Table 1 (continued)

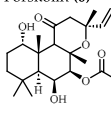
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
				HT-29	IC ₅₀ = 10.18 µM (36 h) IC ₅₀ = 1.39 µM (48 h)	↑ subG ₁ phase ↓ G ₂ /M ↑ caspase 3, 8 and 9, PARP, p53/21 ↓ Bcl-2, Akt, cyclin D1, PCNA PIK3 not altered. ↓ p50 subunit of NF-κB ↑ β-catenin	HCD had a higher potential than conventional chemotherapeutic agent 5-FU	
			<i>In vitro</i> (MTT assay, AO/EB Double Staining, flow cytometry)	T24	Cell death in a time- and concentration-dependent. Cell shrinkage and formation of apoptotic vacuoles (24, 48 and 72 h). Loss of adhesion at 30 and 40 µM. Cell damage at 10 µM (72 h) and 20 µM (48 h).	Early and late apoptosis. ↓ MMP ↑ ROS, cytochrome C release, caspase 3, cleaved PARP-1 and pH2A.X → Bcl-2 Autophagy. ↑ cell cycle arrest ↑ p21, p53, p27Kip1 ↓ CDK2, CDK4, cyclin D1 ↓ pEGFR, pMEK, pERK1/2, pAkt1, pmTOR, P70S6K1, VEGF	↑ 77 genes involved in apoptosis and 23 in autophagy	(Chen et al., 2020)
			<i>In vitro</i> (MTT assay)	ER (-) MDA-MB 231	IC ₅₀ = 15 µM (24 h)	→ S and G ₂ /M cell cycle phase Apoptosis: ↑ Bax, p53 ↓ Bcl-2	→ cell growth dose-dependently (alone or in combination with TMX) More active in ER (-) at high concentrations. Synergy with TMX in triple negative breast cancer cells.	(Velmurugan et al., 2018)
				ER (+) MCF-7	IC ₅₀ = 25 µM (24 h)	No alterations for caspase 8 nor 12.		

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (colony formation, cell spreading MTT, migration and activity assay)	T24	→ cell proliferation → cell adhesion at 10 (21.61 %), 20 (57.89 %), 30 (80.03 %), and 40 (80.71 %) µM. → cell migration at 20 (60 %) µM. → cell invasion at 20 (100 %) µM. (24 h)	Caspase-8 dependent Apoptosis. ↓ cFLIP, HDAC1-3 mRNA. ↓ integrin-FAK signalling pathway. → GSK3β, NF-Kb, pSrc and STAT3 ↓ MMP9		(Chen et al., 2022)
		<i>Justicia insularis</i> T. Anderson (leaves)	<i>In vitro</i> (SRB assay and flow cytometry)	OVCAR-4	IC ₅₀ = 5.7 ± 0.3 µM (72 h)	Extrinsic and intrinsic Apoptosis:	Drug targets: Kinases, nuclear receptors, and primary active transporters. More rigid and selective than (22). SI = 3	(Fadayomi et al., 2021)
				OVCAR-8	IC ₅₀ = 4.4 ± 0.2 µM (72 h)	↑ caspase 3/7, caspase 8 and 9 ↑ early and late apoptosis (concentration dependent)		
				HOE	IC ₅₀ = 12.1 ± 0.1 µM (72 h)			
	16-oxo-cleroda-3,13(14)E-dien-15-oic acid (2) 			OVCAR-4	IC ₅₀ = 16.6 ± 2.8 µM (72 h)	Apoptosis: ↑ caspase 3/7	Drug targets: nuclear receptors, oxidoreductases, and phosphatases (low probability) SI = 2	
				OVCAR-8	IC ₅₀ = 11.8 ± 0.5 µM (72 h)			
				HOE	IC ₅₀ = 22.8 ± 0.7 µM (72 h)			

(continued on next page)

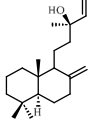
Table 1 (continued)

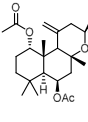
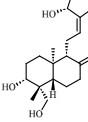
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Haliamine	Crispene E (3) 	<i>Tinospora crispa</i> (L.) Miers ex Hook. f. & Thomson	<i>In vitro</i> (FP, MTT, TBE assay)	MDA-MB-231 (STAT3-dependent)	IC ₅₀ = 5.35 μ M TBE = 85 % cell death (cytotoxicity)	↓ STAT3 and STAT3 dependent genes	STAT3 specific $\downarrow$ by interacting with SH2 domain.	(Mantaj et al., 2015)
	Polyalthic acid (4) 	Donated by Natural Products Research Group of the University of Franca (UNIFRAN) – Can be isolated from <i>Copaifera</i> genus in Africa.	<i>In vitro</i> (XTT assay)	MCF-7	IC ₅₀ (PA) = 751 μ M (24 h) IC ₅₀ (PA-NP) = 270.3 μ M (24 h)	Selective DNA damage of cancer cells induced by PA and enhanced by PA-NP may lead to selective $\downarrow$ of cell proliferation.	PA-NP = polyalthic acid-containing nanoparticles; SI for PA was 0.66 and for PA-NP was 0.59. Selective genotoxicity reported.	(Chibas et al., 2019)
				MCF-10A	IC ₅₀ (PA) = 158.4 μ M (24 h) IC ₅₀ (PA-NP) = 498.2 μ M (24 h)			
	11R*,13E)-11-acetoxyhalima5,13-dien-15-oic acid (5) 	<i>Plectranthus ornatus</i> Codd. (whole plant)	<i>In vitro</i> (MTT assay)	A549	IC ₅₀ = 53.50 μ M (24 h)	↑ ROS production, nDNA damage ↓ Number of mtDNA copies.	Moderate antioxidant activity was reported. ADMET studies demonstrated drug-likeness properties.	(Sitarek et al., 2022a)
				CCRF-CEM	IC ₅₀ = 45.55 μ M (24 h)	Altered MMP.		
				ARPE-19	No cytotoxic effect.	Anti-inflammatory effect through regulation of the expression of genes IL-6, IL-8, TNF- α and GM-CSF.		

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Labdane	Forskolin (6) 	<i>Coleus forskohlii</i> Briq. (roots)	<i>In vitro</i> (MTT assay)	MCF7	IC ₅₀ = 37.67 μ M (24 h)	Apoptosis via the mitochondrial pathway: ↑ mitochondrial accumulation of ROS. ↓ MMP, mtDNA copies. ↑ DNA damage (ND1 and ND5 gene regions), caspase 3/7 activity. Changed expression of pro- and anti-apoptotic genes.		(Sitarek et al., 2022b)
				FaDu	IC ₅₀ = 41.74 μ M (24 h)			
			<i>In vivo</i> (Brine shrimp test)		No toxic effect was reported.		The tested concentration was 100 μ g/mL with 24 h incubation	
			<i>In vitro</i> (MTT assay)	HEI-OC1	↑ cell viability (48 h)	Cisplatin → apoptosis of HEI-OC1 cells via mitochondrial apoptotic pathway. (reverts effects of Cisplatin) $\downarrow$ cisplatin-induced mitochondrial apoptotic pathway and ROS generation in HEI-OC1 cells → ↓ ROS, Bax and caspase-3, ↓ Bcl-2. p38 and ERK/MAPK pathway are involved in the protective effect upon cisplatin exposure.	Could significantly protect against cisplatin-induced cytotoxicity in HEI-OC1 cells.	(Guo et al., 2018)
			<i>In vivo</i> (C57BL/6J mice)		Treatment attenuates cisplatin-induced hearing loss.			

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (CCK-8 assay)	MM.1S	IC ₅₀ = 7.8 μ M (24 h) IC ₅₀ = 3.5 μ M (48 h)	→G2/M phase arrest with ↑ of p-cdc25c, p-cdc2, ↓ cyclin B1 → ↓ cdc25C/cdc2/cyclin B pathway. →mitochondrion dependent apoptosis (↑Bax, Bad, Bim proteins and Bid; ↓Bcl-2 and Bcl-xL; the changes of the mitochondrial membrane potential (MMP); ↑cleaved caspase-9, cleaved caspase-3 and cleaved PARP. Apoptosis: ↓ of p-C-Raf, p-MEK, p-ERK1/2 and p-p90Rsk ↑ of p-PERK, p-eIF2 α and CHOP, ↓ Raf/MEK/ERK pathway and → PERK/eIF2 α /CHOP pathway.	Significantly ↓ MM.1S cells viability in a time- and dose-dependent manner.	(Yang et al., 2021)
	Manool (7) 	<i>Salvia officinalis</i> L. (dried leaves)	<i>In vitro</i> (XTT colorimetric assay)	HeLa U343	IC ₅₀ = 23.06 $\pm$ 3.79 μ M (17 h) IC ₅₀ = 23.06 $\pm$ 4.13 μ M (17 h)		Selective to tumoral cells. SI(HeLa) = 7.4, SI(U343) = 7.4	(de Oliveira et al., 2016)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	1 α ,6 β -diacetoxy-8 α ,13R*-epoxy-14-labden-11-one (8) 	<i>Plectranthus ornatus</i> Codd. (whole plant)	<i>In vitro</i> (MTT assay)	MCF7 FaDu	IC ₅₀ = 41.64 μ M (24 h) IC ₅₀ = 77.76 μ M (24 h)	Significant and sustained ↑ in ROS levels compared to the control group Apoptotic inductive effects to caspase 3/7 activation		(Sitarek et al., 2022b)
	Andrographolide (10) 	<i>Andrographis paniculata</i> (Burm. f.) Nees (leaves and branches)	<i>In vitro</i> (CCK-8, annexin among others)	MDA-MB-231	IC ₅₀ = 77.87 μ M (48 h)	↑Apoptosis (affects cell viability $\geq$ 30 μ M) ↓ cell invasion and migration (10 μ M) ↓MMP-9 at transcriptional level, via the ↓ of I κ B α phosphorylation → ↓ NF- κ B signalling		(Zhai et al., 2015)
			<i>In vivo</i> (tumour xenograft growth of MDA-MB-231 in BALB/c nu/nu mice assay)		↓ breast cancer bone metastasis and osteolysis (50 mg/kg)			
			<i>In vitro</i> (ATPLite luminescence assay)	A549 NCI-H1795	↓ proliferation in both cell lines in time- and dose-dependent manner	↑ p21 and p27 in A549 Senescence (via p53/p21 and Skp2/p27) G1 phase (A549) and G2 cell cycle arrest ↓Proliferation (↓Ki-67)		(Zhang et al., 2022)

(continued on next page)

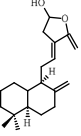
Table 1 (continued)

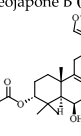
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vivo</i> (tumour xenograft growth of A549 cells in BALB/c nude female mice assay)		Reduction in tumor volumes and weights of the treated groups in a dose-dependent manner, when compared to the control group.	↑ p21 and p27 in A549 -Proliferation (↓Ki-67)	Compound was well tolerated as there was no substantial loss of body weight of mice treated with AD in comparison with the control group.	
			<i>In vitro</i> (CCK-8 assay)	MDA-MB-231	IC ₅₀ = 20.3 ± 2.35 μM (48 h)	↑Caspase-dependent apoptotic signalling pathway (↑ Cyt. C, cleaved caspase-3/9, Bax and ↓Bcl-2)		(Peng et al., 2018)
				MCF-7	IC ₅₀ = 35.1 ± 3.62 μM (48 h)			
				T47D	IC ₅₀ = 32.4 ± 4.58 μM (48 h)	-binding of the transactivators CREB2, C-Fos and NF-κB (↓COX-2) and blocked the recruitment of coactivator p300 to COX-2 promoter.		
				MDA-MB-361	IC ₅₀ = 31.5 ± 2.98 μM (48 h)			
				BT549	IC ₅₀ = 23.2 ± 1.86 μM (48 h)	-↑ p300 HAT activity, thereby attenuating the p300-mediated acetylation of NF-κB. -↑ migration, invasion and tubulogenesis of HUVECs (↓COX-2 → ↓VEGF).		
			<i>In vitro</i> (wound healing assay)	Ras/Luc	-↑ migration of Ras-transformed cells.			(Yu et al., 2018)
			<i>In vivo</i> (Tumor xenograft growth of		10 μM combined with radiation (2 Gy)	The combination synergistically ↑ MMP-2 activity (-↑ the metastasis),	No significant alterations in body weight were detected	

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			Ras/Luc cell line in BALB/c nude male mice assay)		demonstrated an -↑ effect on cancer metastasis	phospho-ERK 1/2 activity, but only slightly ↓ activation of NF-κB p65 → Decrease cell migration and invasion	following andrographolide and/or radiation treatment.	
			<i>In vitro</i> (Western Blot)	MDA-MB-231	↓ phospho-p65 levels	↓ phospho-p65 levels, p65 activation, -NFκβ signalling ↑ caspase-8 Prevents the degradation of ECM → ↓ MMPs and ↑ TIMP-1. Might -↑ metastasis of cancer cells.	-↑ apoptosis → ↑ FLIP and XIAP	(Beesetti et al., 2019)
			<i>In vitro</i> (Western Blot)	SKOV-3	↓ phospho-p65 levels IC ₅₀ = 54.5 μM (24 h)	↓ phospho-p65 levels, p65 activation, -NFκβ signalling ↑ caspase-8 Prevents the degradation of ECM → ↓ MMPs and ↑ TIMP-1. Might -↑ metastasis of cancer cells.	-↑ apoptosis → ↑ FLIP and XIAP	(Beesetti et al., 2019)
			<i>In vitro</i> (Microspectrofluorometry method MTT method, Western blot, NH ₄ Cl prepulse technique)	HeLa	IC ₅₀ = 10.1 μM (48 h) * ≥100 μM to affect viability of End1 cells, and Ect1 cells.	↓ NHE1, V-ATPase, PARP, pro-Caspase-3, Bcl-2. -MMP. ↓ Cell migration	NHE1 Na ⁺ /H ⁺ Exchanger 1, is a H ⁺ -equivalent extruders which is activated when intracellular pH decreases (pH _{intracellular} < 7.1) as happens in some tumoral cells.	(Loh et al., 2020)
			<i>In vitro</i> (MTT assay)	SAS	↓ Cell viability decreased significantly in a concentration- and time-dependent manner (24, 48, 72 h)	G2/M cell cycle arrest. ↑Intrinsic apoptosis (↓Ψm, ↑ DcR2, DcR3, and DR5 expression. ↑ caspase -8, -9, -		(Liu et al., 2019)

(continued on next page)

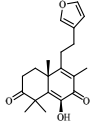
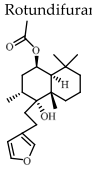
Table 1 (continued)

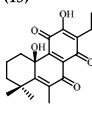
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
						3, PARP, Bak, t-Bid, ↓ Bcl-xL, Bcl-2). ↓activation of ERK1/2, p-38, and AKT, ↑ JNK1/2 activation.		
	Coronarin D (11) 	<i>Hedychium coronarium</i> J. Koenig (roots)	<i>In vitro</i> (MTT assay) <i>In vitro</i> (Sulforhodamine B assay)	SCC-9 U-251	↓ Cell viability decreased significantly in a concentration- and time-dependent manner (24, 48, 72 h) $IC_{50} = 18.6 \pm 0.5 \mu M$ (48 h)	G2/M cell cycle arrest. ↑Intrinsic apoptosis (↓Ψm, ↑ DcR2, DcR3, and DR5 expression. ↑ caspase -8, -9, -3, PARP, Bak, t-Bid, ↓ Bcl-xL, Bcl-2). ↓activation of ERK1/2, p-38, and AKT, ↑ JNK1/2 activation. Cell cycle arrest at G1 phase, in a concentration-dependent way and independent of time exposure. ↑Intrinsic apoptosis (↑H ₂ O ₂ , ↓MMP, ↑ caspases -3, -7, -9, PARP, p21; ↓ERK. ↑ cell death characterized by phosphatidylserine exposure, being a type of programmed cell death.)		(Liu et al., 2019) (Franco et al., 2019)
			<i>In vitro</i> (Sulforhodamine B assay) <i>In vitro</i> (MTT assay)	786-0 PC-3 OVCAR-3 Panc-1	$IC_{50} = 36.4 \pm 4.2 \mu M$ (48 h) $IC_{50} = 17.1 \pm 0.6 \mu M$ (48 h) $IC_{50} = 41.6 \pm 2.1 \mu M$ (48 h) $IC_{50} = 170.6 \pm 3.7 \mu M$ (48 h)	Cell cycle arrest at G1 phase, in a concentration-dependent way and independent of time exposure.	No body weight loss was observed in any mouse and the body weights were similar among all groups.	(Franco et al., 2019) (Yue et al., 2020)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
						↑Intrinsic apoptosis (↑H ₂ O ₂ , ↓MMP, ↑ caspases -3, -7, -9, PARP, p21; ↓ERK. ↑ cell death characterized by phosphatidylserine exposure, being a type of programmed cell death.) ↓ IL-10, IFN γ , ↓NO, IL-6 (immune mediators)	The spleen weight of tumour-bearing mice was significantly increased, which was caused by the tumour burden. Reduced enlarged spleens, the tumour volume and weight as compared with untreated control group.	
	leojapone B (12) 	<i>Leonurus japonicus</i> Houtt. (aerial parts)	<i>In vitro</i> (MTT assay) <i>In vivo</i> (Lung tumour-bearing mouse model-Males C57BL/6)	A427 LLC	$IC_{50} = 39.3 \pm 1.3 \mu M$ (48 h) $IC_{50} = 32.5 \pm 2.4 \mu M$ (48 h) Treatment with 20 and 30 mg/kg leojapone B ↓ tumour weight by 29.4 and 36.2%, respectively, as compared with the control group.	↓ IL-10, IFN γ , ↓NO, IL-6 (immune mediators)	No body weight loss was observed in any mouse and the body weights were similar among all groups. The spleen weight of tumour-bearing mice was significantly increased, which was caused by the tumour burden. Reduced enlarged spleens, the tumour volume and weight as compared with untreated control group. Immunomodulatory activity	(Yue et al., 2020) (Gong et al., 2021)
			<i>In vitro</i> (MTT assay)	MCF-7	$IC_{50} = 97.5 \pm 3.9 \mu M$ (48 h)	↓ IL-10, IFN γ , ↓NO, IL-6 (immune mediators)		

(continued on next page)

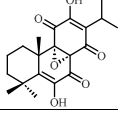
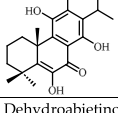
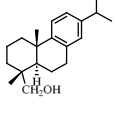
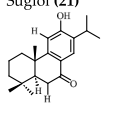
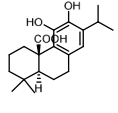
Table 1 (continued)

Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References		
		Heteronone B (13) 		<i>In vitro</i> (MTT assay)	HT-29	IC ₅₀ = 282.5 ±6.9 μM (48 h)	↓ IL-10, IFNγ, ↓NO, IL-6 (immune mediators) ↑Intrinsic apoptosis (↑ROS, ↓MMP; ↑ cleaved caspase-3, cleaved caspase-8, and cleaved caspase-9, Bcl-2 and Bcl-xL, Apaf-1, PARP, → MAPK and PI3K/Akt signal pathways. ↑JNK and ↓phosphorylation PI3K, AKT, ERK) Cell cycle arrest in the G2/M phase	Immunomodulatory activity			
					Panc-1	IC ₅₀ = 65.6 ± 2.4 μM (48 h)					
					DU145	IC ₅₀ = 128.8 ± 3.3 μM (48 h)					
					A427	IC ₅₀ = 105.2 ± 3.7 μM (48 h)					
					LLC	IC ₅₀ = 140.5 ± 3.8 μM (48 h)					
						<i>In vitro</i> (CCK-8 assays)	HeLa	IC ₅₀ = 8.67 μM (24 h), 6.15 μM (48 h)			
				Rotundifuran (14) 	<i>Vitex trifolia</i> L. (fruits)	<i>In vitro</i> (CCK-8 assays) <i>In vivo</i> (HeLa cell inoculated Male BALB/C nude mice xenograft model)	SiHa	IC ₅₀ = 7.29 μM (24 h), 5.49 μM (48 h)	↑Intrinsic apoptosis (↑ROS, ↓MMP; ↑ cleaved caspase-3, cleaved caspase-8, and cleaved caspase-9, Bcl-2 and Bcl-xL, Apaf-1, PARP, → MAPK and PI3K/Akt signal pathways. ↑JNK and ↓phosphorylation PI3K, AKT, ERK) Cell cycle arrest in the G2/M phase Apoptosis <i>in vivo</i> Potential target is Cyr61 and CCAR1		(Gong et al., 2021) (Ntungwe et al., 2022)
								→ Tumor growth			

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (MTT viability assay, Rho123 Accumulation Assay)	NCI-H460	IC ₅₀ = 22.96 ± 0.56 μM (48 h)	Acetone extract ↑ P-gp expression in NCI-H460/R cells and ABCB1 expression in a concentration-dependent manner. ↓ Rho123 accumulation in NCI-H460/R cells. Coleon U and Coleon U quinone at 5 μM sensitize NCI-H460/R cells to DOX.		
TRICYCLIC	Abietane 	Plectranthus mutabilis Codd. (leaves)	<i>In vitro</i> (MTT viability assay, Rho123 Accumulation Assay) <i>In vitro</i> (NDM, quantitative real time migration assay, Western blot analysis, among others)	NCI-H460/R	IC ₅₀ = 20.37 ± 0.43 μM (48 h)	Acetone extract ↑ P-gp expression in NCI-H460/R cells and ABCB1 expression in a concentration-dependent manner. ↓ Rho123 accumulation in NCI-H460/R cells. Coleon U and Coleon U quinone at 5 μM sensitize NCI-H460/R cells to DOX. ↑ Akt/mTOR/autophagy signalling pathway ↓ Autophagy regulators (Atg5, Atg7, Atg12, LC3-I, and LC3-II)	(4) possess anti-metastatic properties even after brief exposure to non-cytotoxic concentrations.	(Ntungwe et al., 2022) (Phan et al., 2022)
				NCI-H460	IC ₅₀ = 20.23 ± 0.59 μM (48 h)			

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	8α,9α-epoxycoleon-U-quinone (16) 			NCI-H460/R	IC ₅₀ = 17.26 ± 0.26 μ M (48 h)			
				NCI-H460	IC ₅₀ = 14.11 ± 0.19 μ M (48 h)			
	Coleon U (17) 			NCI-H460/R	IC ₅₀ = 14.50 ± 0.18 μ M (48 h)			
				MIA PaCa-2	PC ₅₀ = 6.6 μ M (24 h)			
	Dehydroabietinol (18) 	<i>Abies spectabilis</i> (D. Don) Mirb. (stems)	<i>In vitro</i> (MTT assay, Annexin-V/PI staining, western blot among others)	HEC-1-A	IC ₅₀ = 14 μ M (48 h)	↑Apoptosis (↓Bax, ↓Bcl-2) ↑Autophagy (-LC3B-II, Beclin-1, Atg5, Atg12; ↓P62) Sugiol-treated HEC-1-B cells demonstrated membrane blebbing, DNA fragmentation, and formation of ↑apoptotic crops apoptotic (early and late) and necrotic cells in comparison to control group. Sugiol retards the migration and invasion of endometrial carcinoma cells.		(Zhao and Zhang, 2021)
	Sugiol (21) 	Purchased from BioCrick Biotech Co. Ltd Sichuan, China – Can be isolated from <i>Juniperus formosana</i> Hayata, and <i>Metasequoia glyptostroboides</i> Hu & W.C.Cheng in Africa	<i>In vitro</i> (MTT assay, Annexin-V/PI staining, western blot among others) <i>In vitro</i> (colorimetric cytotoxicity assessment- WST-8 reagent, Mitochondrial ToxGlo Assay)	HEC-1-B KLE PANC-1	IC₅₀ = 14 μM (48 h) IC₅₀ = 16 μM (48 h) EC₅₀: 9.0 μM (Glc-), 243 μM (Glc+) (48 h)	↑Apoptosis (↓Bax, ↓Bcl-2) ↑Autophagy (-LC3B-II, Beclin-1, Atg5, Atg12; ↓P62) Sugiol-treated HEC-1-B cells demonstrated membrane blebbing, DNA fragmentation, and formation of ↑apoptotic crops apoptotic (early and late) and necrotic cells in comparison to control group. Sugiol retards the migration and invasion of endometrial carcinoma cells. ↑ ROS production ↑ JNK pathway ↑ Bax, Bak, Bad, Cyto-C ↑Cleaved caspase 3 and 9 G2/M Cell cycle arrest	→ tumour proliferation and → apoptosis both <i>in vitro</i> (30 μM) and <i>in vivo</i> (30 mg/kg). → progression and development of cervical cancer tumors.	(Zhao and Zhang, 2021) (Su et al., 2016)
	Carnosic acid (22) 	<i>Rosmarinus officinalis</i> L.	<i>In vitro</i> (MTT assay, colony formation assay, Boyden chamber assay)	CaSki	Decreasing of cell growth rate in a time- and dose-dependent manner (24, 48 and 72 h) → cell proliferation in a concentration-dependent manner → cervical cancer cells migration in a dose-dependent manner	↑ ROS production ↑ JNK pathway ↑ Bax, Bak, Bad, Cyto-C ↑Cleaved caspase 3 and 9 G2/M Cell cycle arrest ↓ Akt/NF-κB and Akt/Bad signaling pathways	→ tumour proliferation and → apoptosis both <i>in vitro</i> (30 μM) and <i>in vivo</i> (30 mg/kg). → progression and development of cervical cancer tumors.	(Su et al., 2016) (Tang et al., 2016)

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (MTT assay, colony formation assay, Boyden chamber assay) <i>In vivo</i> (BALB/c Akt-knockout mice model - 20 mg/kg by intraperitoneal injection, 4 weeks)	SiHa MHCC97-H	Decreasing of cell growth rate in a time- and dose-dependent manner (24, 48 and 72 h) → cell proliferation in a concentration-dependent manner → cervical cancer cells migration in a dose-dependent manner ↓ tumor volume and size.		Prevention of liver cancer progression → apoptosis both <i>in vitro</i> and <i>in vivo</i>	
			<i>In vivo</i> (BALB/c Akt-knockout mice model - 20 mg/kg by intraperitoneal injection, 4 weeks) <i>In vitro</i> (MTT assay up to 10 days)	Bel7402 SKBR-3	↓ tumor volume and size. Inhibits cell survival and migration	↓ Akt/NF-κB and Akt/Bad signaling pathways ↓ ERBB2 ↓ PI3K/AKT/mTOR ↑ CDKN1A/p21 ^{WAF1} ↑ CDKN1B/p27 ^{KIP1} ↑ SQSTM1/p62	Prevention of liver cancer progression → apoptosis both <i>in vitro</i> and <i>in vivo</i> Cooperation between CA and Trastuzumab (Tz): → cell migration and survival of ERBB2+ cells → cell cycle arrest in G0/G1 and ↓ the ERBB2+ cells fraction in G2/M	(Tang et al., 2016) (D'Alesio et al., 2017)
		<i>Salvia somalensis</i> (aerial parts)	<i>In vitro</i> (MTT assay up to 10 days) <i>In vivo</i> (B16F10 cell xenograft model- 50 mg/kg)	BT474 SKBR-3 Tz-resistant cell line	Inhibits cell survival and migration Significant growth →	↓ ERBB2 ↓ PI3K/AKT/mTOR ↑ CDKN1A/p21 ^{WAF1} ↑ CDKN1B/p27 ^{KIP1} ↑ SQSTM1/p62 ↑ p21	Cooperation between CA and Trastuzumab (Tz): → cell migration and survival of ERBB2+ cells	(D'Alesio et al., 2017) (Lin et al., 2018)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			each 2 days by intraperitoneal injection, 12 days)			Significant growth → and cell cycle arrest at G0/G1 phase	→ cell cycle arrest in G0/G1 and ↓ the ERBB2+ cells fraction in G2/M Synergism with carmustine and lomustine	
		Supplied by ChemFaces (Wuhan, Hubei, China) – Can be isolated from <i>Rosmarinus officinalis</i> L. in Africa	<i>In vitro</i> (MTT assay, BrdU assays) <i>In vivo</i> (Mouse LLC (Lewis lung cancer) xenografts - 10 mg·kg ⁻¹ per day by gavage once daily for 16 days)	B16F10	IC ₅₀ = 7.08 ± 0.14 μM (24 h, MTT) IC ₅₀ = 8.64 ± 1.02 μM (24 h, BrdU) → myeloid-derived suppressor cells	↑ p21 Significant growth → and cell cycle arrest at G0/G1 phase ↑ Function of CD8 ⁺ T ↑ IFN-γ secretion ↑ FasL ↑ Perforin ↑ granzyme B	Synergism with carmustine and lomustine Enhances the anti-lung cancer effect of cisplatin	(Lin et al., 2018) (Liu et al., 2018)
			<i>In vitro</i> (MTT assay)	AGS	IC ₅₀ = 49.85 μM (72 h)	↓ PI3K/Akt/mTOR pathway ↓ Survival	→ apoptosis and → Akt/mTOR Signaling	(El-Huneidi et al., 2021)
			<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTT assay)	MKN-45 KYSE-150	IC ₅₀ = 53.42 μM (72 h) IC ₅₀ = 29.87 ± 4.38 μM (48 h)	↓ PI3K/Akt/mTOR pathway ↓ Survival ↓ MDM2, cyclin B1, and CDC2 ↓ ERK, p38, and JNK signaling pathways ↓ Bcl2 ↑ Bax. Cleaved Casp. 3	→ apoptosis and → Akt/mTOR Signaling CA dose-dependently → cell proliferation, migration, and colony formation. → apoptosis	(El-Huneidi et al., 2021) (S. Jiang et al., 2021)

(continued on next page)

Table 1 (continued)

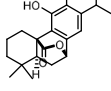
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (MTT assay)	BAEC	IC ₅₀ = 36.30 ± 2.50 µM (72 h)	↓ MMP-2		(López-Jiménez et al., 2013)
			<i>In vitro</i> (MTT assay)	HUVEC	IC ₅₀ = 36.00 ± 1.10 µM (72 h)	↓ MMP-2	Changes in morphology in the CAM neovascularization (↓ vascular density and centrifugal growth of the peripheral vessels)	(López-Jiménez et al., 2013) (Mahmoud et al., 2020)
			<i>In vivo</i> (Chick chorioallantoic membrane assay- 5 nmol in Methylcellulose disk c, 48 h)	HL-60	IC ₅₀ = 5.70 ± 0.70 µM (72 h)			
				HT-1080	IC ₅₀ = 6.60 ± 2.30 µM (72 h)			
					– <i>in vivo</i> angiogenesis, 100% total inhibition at 5 nmol/CAM.			
			<i>In vitro</i> (Resazurin assay, FITC Annexin V/PI apoptosis assay, ROS determination, western blot)	MDR cell lines expressing ABC transporters (P-gp, BCRP, or ABCB5).	No cross-resistance to (89).		Results indicate that (89) could be used to overcome resistance and effectively inhibit cells that would otherwise be drug-resistant, with similar efficacy to drug-sensitive tumor cells.	

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (Resazurin assay, FITC Annexin V/PI apoptosis assay, ROS determination, western blot)	MDR cell lines expressing oncogenes (mutant EGFR)	No cross-resistance to (89). Volume inhibition of 27.2%, 26.4% and 24.4%.	↑metabolic-related gene GCNT3 ↓miR-15b	Results indicate that (89) could be used to overcome resistance and effectively inhibit cells that would otherwise be drug-resistant, with similar efficacy to drug-sensitive tumor cells. Potential to be used as a complementary approach in colon and pancreatic cancer. No toxicity detected.	(González-Vallinas et al., 2014) (Mahmoud et al., 2020)
			<i>In vivo</i> (Nude mice bearing SW620 colon cancer xenografts; 1 mg extract and 20 µL ethanol per mL of drinking water, 32–35 days).	MDR cell lines expressing p53				
	Carnosic acid-rich extract	<i>Rosmarinus officinalis</i> L. (leaves)	<i>In vitro</i> (MTT assay, western blot)	PANC-1	Most resistant to the extract.	↑metabolic-related gene GCNT3 ↓miR-15b ↑ Nrf2/sestrin-2 pathway	Potential to be used as a complementary approach in colon and pancreatic cancer. No toxicity detected.	(González-Vallinas et al., 2014) (Yan et al., 2015)
			<i>In vitro</i> (MTT assay, western blot)	MIA-PaCa-2	Resistant to the extract.			
				SW620	Sensitive to the extract.			
			<i>In vitro</i> (MTT assay)	DLD-1	Sensitive to the extract. Tumor cell death induced at 70 µg/mL (48 h).			
				HCT116	Cell viability decreased in a dose and time-		Colon cancer cells were more sensitive than pancreatic cancer cells.	

(continued on next page)

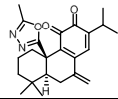
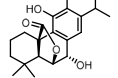
Table 1 (continued)

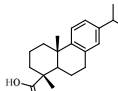
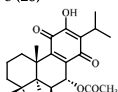
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
					dependent manner (24, 48 and 72 h)		→ apoptosis, and ↓ viability in colon cancer cell lines. <i>In vivo</i> dose was well tolerated.	
		<i>Rosmarinus officinalis</i> L. Extract obtained from P. L. Thomas & Co., Inc. (Morristown, NJ, USA. Lot: 3494301)	<i>In vitro</i> (MTT assay) <i>In vivo</i> (HCT116 tumor xenograft mice model - 100 mg/kg) in by oral gavage 7 days weekly	SW480	Cell viability decreased in a dose and time-dependent manner (24, 48 and 72 h) → a HCT116 xenograft tumor formation in mice, → tumor growth.	↑ Nrf2/sestrin-2 pathway ↓ MAPK ↓ NLRP3 ↓ SREBF1	→ apoptosis, and ↓ viability in colon cancer cell lines. <i>In vivo</i> dose was well tolerated. Reduces lipid metabolism. Synergises with therapeutic drugs used in the clinic. ↓ lipid metabolic and inflammatory targets in PBMC	(Yan et al., 2015) (Bouzas et al., 2022)
			<i>In vitro</i> (MTT assay)	NCI-H1299	IC ₅₀ = 42.14 ± 0.926 µg/mL (48 h)			
		<i>Rosmarinus officinalis</i> L. (leaves)	<i>In vitro</i> (MTT assay) <i>In vivo</i> (C26 tumour-bearing BALB/c mice- 10 mg/kg (carnosol, 20 mg/kg (DCSD), daily intraperitoneal injections)	NCI-H1975	IC ₅₀ = 52.19 ± 0.614 µg/mL (48 h) Alleviate cancer cachexia. Improvement of the decrease in body weight: higher by 11.09% than that of the untreated group. Improvement of myofiber atrophy, fat degradation.	↓ MAPK ↓ NLRP3 ↓ SREBF1 ↓ NF-κB pathway ↓ AMPK pathway ↑ AKT pathway	Reduces lipid metabolism. Synergises with therapeutic drugs used in the clinic. ↓ lipid metabolic and inflammatory targets in PBMC Dose-dependent protective effects on muscle atrophy of C2C12 myotubes. Reduction of muscle atrophy.	(Bouzas et al., 2022) (Lu et al., 2021)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Carnosol (23) 	Purchased from Shanghai NatureStandard Biotechnology Co., LTD (Shanghai, P.R. China) – Can be isolated from <i>Rosmarinus officinalis</i> L. in Africa	<i>In vitro</i> (MTT assay)	Cell models of C2C12 myotube atrophy and 3T3-L1 mature adipocyte lipolysis	Cytotoxic at doses higher than 25 µM (48 h)	↓ NF-κB pathway ↓ AMPK pathway ↑ AKT pathway In combination with curcumin: ↓ Akt and STAT3 phosphorylation; ↓ EGF-induced invasion and metastasis	Dose-dependent protective effects on muscle atrophy of C2C12 myotubes. Reduction of muscle atrophy. Carnosol → EGF-induced invasion and metastasis in human ovarian cancer cells Synergism with curcumin.	(Lu et al., 2021) (Vergara et al., 2014)
			<i>In vitro</i> (MTT assay)	SKOV-3	IC ₅₀ > 50 µM (24, 48 and 72 h)			
		Purchased from Sigma-Aldrich – Can be isolated from <i>Rosmarinus officinalis</i> L. in Africa	<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTS assay)	MDA-231 Primary tumour cells from patients with lung, ovarian and endometrial cancer U87MG	IC ₅₀ > 50 µM (24, 48 and 72 h) IC ₅₀ > 50 µM (24, 48 and 72 h) IC ₅₀ = 10.40 ± 0.50 µM (72 h)	In combination with curcumin: ↓ Akt and STAT3 phosphorylation; ↓ EGF-induced invasion and metastasis ↓ Cell proliferation and invasiveness ↓ MDM2/p53 complex ↑ p53 pathway Synergistic effects with temozolomide (TMZ)	Carnosol → EGF-induced invasion and metastasis in human ovarian cancer cells Synergism with curcumin. ↓ proliferation, invasiveness, and resistance to therapy of U87MG cells. → apoptosis and cell cycle block. Selectivity towards the tumour cell.	(Vergara et al., 2014) (Giacomelli et al., 2016)
			<i>In vitro</i> (MTS assay)	U87MG	IC ₅₀ = 14.9 µM (48 h)	↓ CD44 gene. ↑ Intracellular p53 levels ↓ BMI1 expression	Carnosol controls the human glioblastoma stemness features through the epithelial	(Giacomelli et al., 2017)

(continued on next page)

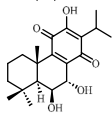
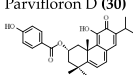
Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
							mesenchymal transition. modulation and the → cancer stem cell apoptosis.	
			<i>In vitro</i> (MTT assay)	PANC-1	EC ₅₀ = 50.50 ± 6.6 μM (72 h)	HsFPPS inhibition	Active in pancreatic cancer cell killing were it acts by targeting HsFPPS	(Han et al., 2019)
	Carnosic acid derivative 81 CA28a (24) 	Synthetic derivative of carnosic acid	<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTT assay)	MIA PaCa-2 MCF-7	EC ₅₀ = 50.50 ± 6.6 μM (72 h) IC ₅₀ = 19 μM (72 h)	HsFPPS inhibition ↓ ERK and STAT3 signals ↑ p-p38 ↓ PI3K/AKT ↓ ERK ↓ JAK2/STAT3	Active in pancreatic cancer cell killing were it acts by targeting HsFPPS → proliferation and → apoptosis and cell cycle arrest.	(Han et al., 2019) (D. Jiang et al., 2021)
	Rosmanol (26) 	Supplied by Baoji Herbest Bio-tech Co., Ltd. – Can be isolated from <i>Rosmarinus officinalis</i> L., and <i>Salvia officinalis</i> L. in Africa	<i>In vitro</i> (MTT assay) <i>In vitro</i> (WST-8 assay, RNA sequencing, Annexin V-FITC/PI Apoptosis Assay, PCR, Western Blot)	MDA-MB 231 AGS	IC ₅₀ = 16 μM (72 h) → cell growth (higher rate 48 h > 24 h time- and dose-dependent manner)	↓ ERK and STAT3 signals ↑ p-p38 ↓ PI3K/AKT ↓ ERK ↓ JAK2/STAT3 ↓ Gene Expression Related to Cell Proliferation ↓ basal level expression ↓ overexpressed proteins. ↑ Apoptosis (↑Bax and PARP)	→ proliferation and → apoptosis and cell cycle arrest. (7) has a better inhibitory effect than the surviving inhibitor YM-155.s. Depending on the cell line, change in the stage on which the apoptosis is induced	(D. Jiang et al., 2021) (Kim et al., 2021)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Dehydroabietic acid (27) 	<i>Pinus</i> spp. (resin)	<i>In vitro</i> (WST-8 assay, RNA sequencing, Annexin V-FITC/PI Apoptosis Assay, PCR, Western Blot) <i>In vitro</i> (Alamar blue assay, fluorescence microscopy)	MKN-28 SNU-216 SNU-601 SNU-668 YCC-2 U87	→ cell growth (higher rate 48 h > 24 h time- and dose-dependent manner) IC ₅₀ = 104.95 μM (24 h) IC ₅₀ = 59.39 μM (48 h) IC ₅₀ = 18.21 μM (72 h)	↓ Gene Expression Related to Cell Proliferation ↓ basal level expression ↓ overexpressed proteins. ↑ Apoptosis (↑Bax and PARP) ↑ Intrinsic apoptosis.	(7) has a better inhibitory effect than the surviving inhibitor YM-155.s. Depending on the cell line, change in the stage on which the apoptosis is induced	(Kim et al., 2021) (Dominguez-Martin et al., 2022) (Magalhães et al., 2022)
	7α-acetoxy-6β-hydroxyroyleanone (28) 	<i>Plectranthus hadiensis</i> (Forssk.) Schweinf. ex Sprenger var. <i>hadiensis</i> (stems)	<i>In vitro</i> (Alamar blue assay, fluorescence microscopy) <i>In vitro</i> (Alamar blue assay, fluorescence microscopy, flow cytometry, quantitative real-time PCR)	A172 U118 U373 H4 U118	IC ₅₀ = 119.80 μM (24 h) IC ₅₀ = 84.64 μM (48 h) IC ₅₀ = 67.38 μM (72 h) IC ₅₀ = 19.57 μM (24 h) IC ₅₀ = 22.64 μM (48 h) IC ₅₀ = 20.59 μM (72 h) IC ₅₀ = 16.06 μM (24 h) IC ₅₀ = 15.90 μM (48 h) IC ₅₀ = 145.74 μM (24 h) IC ₅₀ = 46.33 μM (48 h) IC ₅₀ = 33.27 μM (72 h) IC ₅₀ = 48.79 μM (24 h) IC ₅₀ = 16.72 μM (48 h) IC ₅₀ = 34.64 μM (72 h)	↑ Intrinsic apoptosis. ↑ Intrinsic apoptosis (-MMP, Bax/Bcl-2 ratio, PTEN, P53).	<i>In vivo</i> assays on-going	(Dominguez-Martin et al., 2022) (Magalhães et al., 2022)

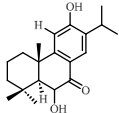
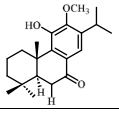
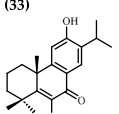
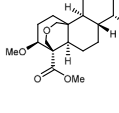
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	6α,7 β-dihydroxyroyleanone (29) 			U373	IC ₅₀ = 164.76 μ M (24 h) IC ₅₀ = 96.72 μ M (48 h) IC ₅₀ = 55.39 μ M (72 h)			
				U87	IC ₅₀ = 11.28 μ M. (48 h)			
	Parvifloron D (30) 	<i>Plectranthus ecklonii</i> Benth. (aerial parts)	<i>In vitro</i> (Alamar blue assay, fluorescence microscopy, flow cytometry, quantitative real-time PCR) <i>In vitro</i> (colorimetric cytotoxicity assessment- WST-8 reagent, Mitochondrial ToxGlo Assay)	A172	IC ₅₀ = 72.01 μ M (48 h)	↑ Intrinsic apoptosis (-MMP, Bax/Bcl-2 ratio, PTEN, going P53). 6α-hydroxysugiol ↓ the intracellular ATP levels in a dose-dependent manner Selective cytotoxicity via mitochondrial function ↓	<i>In vivo</i> assays on-	(Magalhães et al., 2022) (Zaher et al., 2020)
				U118	IC ₅₀ = 1.22 μ M (48 h)			
				U373	IC ₅₀ = 59.68 μ M (48 h)			
				H4	IC ₅₀ = 12.47 μ M (48 h)			
				PANC-1	EC ₅₀ = 9.0 μ M (Glc-), 243 μ M (Glc+) (48 h)			

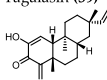
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	6 α -hydroxysugiol (31) 	<i>Taxodium distichum</i> (L.) Rich (bark)	<i>In vitro</i> (colorimetric cytotoxicity assessment- WST-8 reagent, Mitochondrial ToxGlo Assay) <i>In vitro</i> (MTT assay, Caspase-3 activity and Western blotting analysis)	PANC-1 HL-60	EC ₅₀ = 37.9 μ M (Glc-), 303 μ M (Glc+) (48 h)	6 α -hydroxysugiol $\downarrow$ the intracellular ATP levels in a dose-dependent manner Selective cytotoxicity via mitochondrial function $\rightarrow$ $\uparrow$ proteolytic cleavage of procaspase-3 into its active form $\uparrow$ caspase-3 activity from 10 to 30 mM	(19) is one of the main active components of the seed of <i>C. sappan</i> leading to apoptotic cell death.	(Zaher et al., 2020) (Tran et al., 2015)
	Cryptojaponol (32) 				EC ₅₀ = 6.4 μ M (Glc-), 114 μ M (Glc+) (48 h)			
	6-hydroxy-5,6-dehydrosugiol (33) 				IC ₅₀ = 11.7 $\pm$ 1.6 μ M (48 h)			
Cassaine	Phanginin D (38) 	<i>Caesalpinia sappan</i> L. (seeds)	<i>In vitro</i> (flow cytometry, Western blot analysis, comet assay)	Molt-4	IC ₅₀ = ~1 μ M (48 h)	Apoptotic cell death via ROS-mediated DNA damage, activate the DNA-damage sensor kinases ATM and ATR. Cell cycle arrest at the S-G2 phase.		(Neumann et al., 2015)

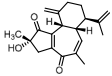
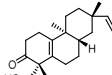
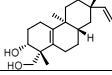
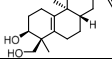
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Dolabrane		Ceriops tagal (Perr.) C.B. Robinson (stems and twigs)	<i>In vitro</i> (flow cytometry, Western blot analysis, comet assay)	SupT1 CEM Jurkat L1236 KM-H2	IC ₅₀ = ~1 μM (48 h) After 14 days, either no tumour growth or reduction in tumour weight, without significant adverse effects	Apoptotic cell death via ROS-mediated DNA damage, activate the DNA-damage sensor kinases ATM and ATR. Cell cycle arrest at the S-G2 phase.		(Neumann et al., 2015) (An et al., 2021)
			<i>In vivo</i> (immunodeficient mice xenografted with human CEM leukemic T cells)	U-266 RPMI-8266 AML 50 mg/kg i.p. per day in the first week and three times in second week				
			<i>In vitro</i> (MTT, cytochrome c-releasing apoptosis assay kit and western blot)	Ishikawa	IC ₅₀ = 0.36 ± 0.06 μM (24 h)	Apoptosis, altering mitochondrial membrane permeability. ↓ procaspase-9, and poly (ADP-ribose) polymerase (PARP) ↑ MAPK, ERK1/2, JNK, and p38, Bim and Bax ↓ Bcl-xL		

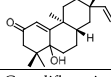
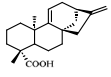
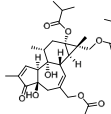
(continued on next page)

Table 1 (continued)

Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Rhamnofolane	Curcosome C (40) 	<i>Jatropha curcas</i> L. (roots)	<i>In vitro</i> (MTT, cytochrome c-releasing apoptosis assay kit and western blot) <i>In vitro</i> (P3HR-1 cells, Burkitt lymphoma cells, infected with EBV latently as described by Cui et al. (2013))	HEC-1A	IC ₅₀ = 0.42 ± 0.03 uM (24 h)	Apoptosis, altering mitochondrial membrane permeability. ↓ procaspase-9, and poly (ADP-ribose) polymerase (PARP) ↑ MAPK, ERK1/2, JNK, and p38, Bim and Bax ↓ Bcl-xL, → EBV lytic replication	→ effects as EC ₅₀ values. Cytotoxicity as CC ₅₀ , SI as CC ₅₀ /EC ₅₀ .	(An et al., 2021) (S. N. Liu et al., 2017)
					P3HR-1	EC ₅₀ = 13.2 μM, CC ₅₀ = 59.6 μM (48 h) and SI= 4.5			
	Rosane	Euphominoid A (41) 	<i>Euphorbia milii</i> Linn. (aerial parts)	<i>In vitro</i> (P3HR-1 cells, Burkitt lymphoma cells, infected with EBV latently as described by Cui et al. (2013)) <i>In vitro</i> (MTT assay)	P3HR-1 MCF-7	EC ₅₀ = 5.4 μM, CC ₅₀ = >50 μM (48 h) and SI= >9.3	→ EBV lytic replication ↑ Intrinsic apoptosis (↑MMP, ROS production, caspase-3 activity) ↑ Autophagy	→ effects as EC ₅₀ values. Cytotoxicity as CC ₅₀ , SI as CC ₅₀ /EC ₅₀ .	(S. N. Liu et al., 2017) (Fagundes et al., 2022)
		Euphominoid B (42) 				EC ₅₀ = 24.4 μM, CC ₅₀ = 113 μM (48 h) SI= 4.6			
		Euphominoid C (43) 				EC ₅₀ = 29.1 μM, CC ₅₀ = >200 μM (48 h) SI= >6.9			

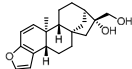
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Euphominoid J (44) 				IC ₅₀ = >0.400 ± 0.00314 μM (24 h)			
TETRACICLYC	Kaurane 	<i>Sphagneticola trilobata</i> (L.) Pruski (roots)	<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTT Cell Viability Assay)	HuH7.5	IC ₅₀ = 0.120 ± 0.00208 μM (24 h)	↑Intrinsic apoptosis (↑MMP, ROS production, caspase-3 activity) ↑Autophagy Activation and nuclear translocation of PKC-δ and PKD as well as hyperactivation of extracellular signal-related kinase (ERK)		(Fagundes et al., 2022) (Tsai et al., 2020)
				A549	IC ₅₀ = 0.170 ± 0.00220 μM (24 h)			
				A549	↓cell viability Maximal ↓ of 49.2% at 0.3 μM (72 h)			
	Tiglane 	<i>Euphorbia grandicornis</i> (aerial parts)	<i>In vitro</i> (MTT Cell Viability Assay) <i>In vitro</i> (LDH assay; Cytotoxicity Detection Kit (Roche Applied Science))	H1299	Growth ↓, but to a lesser extent (72 h)	Activation and nuclear translocation of PKC-δ and PKD as well as hyperactivation of extracellular signal-related kinase (ERK) → ATF-2 and c-Jun, possibly by upstream kinases SAPK/JNK and p38 MAPK. ↑ ↑ CREB mRNA of granzyme B, a cytotoxic effector of NK KHYG-1. ↑ mRNA of cytotoxic effectors perforin, granzyme A and FAS ligand.	LDH released from K562 used to determine NK cell-mediated cytotoxicity. Kahweol at 30 μM. Effector:target (E:T) ratio of 10:1. Strong effect on KHYG-1 cytolytic activity	(Tsai et al., 2020) (Saito et al., 2015)
				MCF-7	Growth ↓, but to a lesser extent (72 h)			
				MDA-MB-231	Cytolytic activity improved 1.4-fold (4 h).			
				KHYG-1 Against (natural killer) NK-sensitive K562				

(continued on next page)

Table 1 (continued)

Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
PENTACYCLIC	Kahweol & Cafestol		Coffea spp.	In vitro (MTT and LDH assay)	HT-29	Significant cytotoxic effect. Morphological alterations at 100 µM and 200 µM (20 h)	↑ expression of caspase-3 ↓ expression of Bcl-2, phosphorylated Akt, and HSP70.	Cancer cells suffered morphological changes, such as rounding and detachment, in a concentration-dependent manner.	(Choi et al., 2015)
				In vitro (MTT assay)	HCT116	Treated with 12.5 µM After 24 h = 16% cell proliferation ↓ After 48 h = 48% cell proliferation ↓ Treated with 25 µM After 24h = 28% cell proliferation ↓ After 48 h = 69% cell proliferation ↓ Treated with 50 µM After 24h = 53% cell proliferation ↓ After 48 h = 99% cell proliferation ↓	Proteasomal degradation of cyclin D1 mediated by the phosphorylation of its threonine 286 residue by kahweol-activated ERK1/2, JNK and GKS-3β.	Normal human colon cells CCD-18Co not affected. Cafestol was less cytotoxic (specific values not reported).	(Park et al., 2017)
				In vitro (MTT assay)	SW480 Human colon cancer cells	Treated with 12.5 µM After 24 h = 8% cell proliferation ↓ After 48 h = 12% cell proliferation ↓ Treated with 25 µM After 24 h = 19% cell proliferation ↓ After 48 h = 38% cell proliferation ↓	Proteasomal degradation of cyclin D1 mediated by the phosphorylation of its threonine 286 residue by kahweol-activated ERK1/2, JNK and GKS-3β. Apoptosis: ↑ ATF3 expression through promoter activation mediated by kahweol.	Normal human colon cells CCD-18Co not affected. Cafestol was less cytotoxic (specific values not reported). ↑ ATF3 expression in a dose-dependent manner.	(Park et al., 2017) (Seo et al., 2018)

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (Western blot against cleaved PARP after transient transfection of cells with ATF3 promoter)		Treated with 50 μ M After 24 h = 38% cell proliferation $\downarrow$ After 48 h = 89% cell proliferation $\downarrow$	Cis-acting element CREB of ATF3 may $\rightarrow$ expression. $\uparrow$ cleaved PARP.		
				HCT116	Treatment with 50 μ M $\uparrow$ cleaved PARP (24 h), $\rightarrow$ Apoptosis			
			<i>In vitro</i> (Western blot against cleaved PARP after transient transfection of cells with ATF3 promoter) <i>In vitro</i> (LPS-stimulated cells detected via ELISA)	SW480	Treatment with 50 μ M $\uparrow$ cleaved PARP (24 h), $\rightarrow$ Apoptosis Anti-inflammatory effect	Apoptosis: $\uparrow$ ATF3 expression through promoter activation mediated by kahweol. Cis-acting element CREB of ATF3 may $\rightarrow$ expression. $\uparrow$ cleaved PARP. $\rightarrow$ STAT3 and MAPK activation. $\rightarrow$ p-JNK and phosho p38 MAPK in primary KC, NF- κ B activation. $\downarrow$ expression of IL1 α , IL1 β , IL6 and TNF α . $\uparrow$ HO-1 levels.	$\uparrow$ ATF3 expression in a dose-dependent manner.	
				LoVo HT-29 Primary Kupffer Cells (KC) and Primary Hepatocytes (HC) C57BL/6				
			<i>In vitro</i> (MTT and LDH assay)	HER2-positive (overexpressing) SKBR3	HER2-overexpressing SKBR3 had higher susceptibility (> 5 μ M) than the other cells lines. SKBR3 cell line was significantly more	Apoptosis: $\uparrow$ caspse-3 and PARP) in HER2-overexpressing SKBR3. Transcriptional modulation of HER2 via modulation of	$\uparrow$ levels of caspse-3 and PARP in HER2-positive SKBR3 cells after treatment with 10–50 μ M) for 24 h. Apoptotic cell death	(Oh et al., 2018)

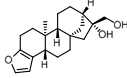
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
					susceptible than others. (24 h)	transcription factors PEA3 and AP-2. ↓ mRNA FASN and promoter activity of SREBP-1c. → phosphorylation of Akt modulates FASN activity. → Cyclin D1 via ↓ phosphorylation of mTOR and GSK-3β.	of HER2-overexpressing SKBR3.	
			<i>In vitro</i> (ROS production measurement via fluorescent dye H ₂ DCFDA, cell viability detected by Cell Counting Kit-8, flow cytometry, western blot, RT-PCR, immunoprecipitation)	AML12	→ H ₂ O ₂ -induced ROS generation (10 or 20 μM, 24 h) → apoptosis in hepatocytes (24 h) ↓ Keap1 protein level, no changes in mRNA, no changes in p62 expression	↓ cleaved caspase 3, ROS significantly. → translation of Keap1 mRNA. ↑ Nrf2 expression which led to ↑ expression of HO-1. HO-1 eliminated ROS. ↓ Keap1 protein expression is independent from the degradation pathway for Keap1	Anti-inflammatory activity.	(Seo et al., 2020)
			<i>In vitro</i> (ROS production measurement via fluorescent dye H ₂ DCFDA, cell viability detected by Cell Counting Kit-8, flow	Hepatocytes from male 6-8-week-old C57BL/6 hepatocyte-specific ATG7-	↓ Keap1 protein expression ↑ expression of HO-1 in primary hepatocytes	↓ cleaved caspase 3, ROS significantly. → translation of Keap1 mRNA. ↑ Nrf2 expression which led to ↑ expression of HO-1. HO-1 eliminated ROS.	Anti-inflammatory activity. LDH released from K562 used to determine NK cell-mediated cytotoxicity. Cafestol at 30 μM. E:T of 10:1.	(Seo et al., 2020) (Saito et al., 2015)

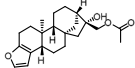
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			cytometry, western blot, RT-PCR, immunoprecipitation) <i>In vitro</i> (LDH assay; Cytotoxicity Detection Kit (Roche Applied Science))	knockout mice KHYG-1 Against NK-sensitive K562	Cytolytic activity improved 1.5-fold (4 h).	↓ Keap1 protein expression is independent from the degradation pathway for Keap1 → ATF-2 and c-Jun, possibly by upstream kinases SAPK/JNK and p38 MAPK. ↑ ↑ CREB mRNA of granzyme B, a cytotoxic effector of NK KHYG-1. ↑ mRNA of cytotoxic effectors perforin, granzyme A and FAS ligand.	Strong effect on KHYG-1 cytolytic activity	
	Cafestol (56) 		<i>In vitro</i> (TBE assay, Cell death evaluation by Annexin V/FITC–PI staining and flow cytometry)	KG1	Viability ↓ with 40–150 μM in a concentration-dependent manner (24 h).	Apoptosis (phosphatidylserine on the outer membrane) via the intrinsic mitochondrial pathway: ↓ MMP, ROS. ↑ cleaved caspase 3, CD11b and CD15 differentiation markers, sub-G accumulation.	HL60 used to understand the molecular mechanism. Synergy with Ara-C. Forced differentiation/maturation can be a therapeutic strategy in leukaemia treatment.	(Lima et al., 2017)
			<i>In vitro</i> (TBE assay, Cell death evaluation by Annexin V/FITC–PI staining and flow cytometry)	HL60 NB4	Viability ↓ with 40–150 μM in a concentration-dependent manner (24 h). Drug resistant cell lines: viability ↓ with 150 μM (24 h).	Apoptosis (phosphatidylserine on the outer membrane) via the intrinsic mitochondrial pathway: ↓ MMP, ROS. ↑ cleaved caspase 3, CD11b and CD15 differentiation	HL60 used to understand the molecular mechanism. Synergy with Ara-C. Forced differentiation/maturation can be a	(Lima et al., 2017) (Al-Kenany and Al-Shawi, 2023)

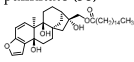
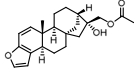
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vivo</i> (Wistar albino experimental rats; one control group (I), one group cafestol only (II), one group DOX only (III) and one group Cafestol+DOX (IV))	K562 Caki-1	Drug resistant cell lines: viability ↓ with 150 μM (24 h). Chemoprotective effect against DOX	markers, sub-G accumulation. Chemoprotective effect against DOX: ↓ cellular injury biomarkers. Ameliorated histopathological changes. ↓ MDA and ↑ GSH, restoring the activity of SOD, CAT, and GPx-1. -↑ caspase 3 ↑ Bax. Anti-inflammation activity via the NF-κB/Nrf2/HO-1/NQO-1 pathway: ↓ IL-1β, TNF-α, mRNA expression of Keap1.	therapeutic strategy in leukaemia treatment. Similar results for groups I and II. Comparison of group III and IV demonstrated that cafestol had a chemoprotective effect against DOX-induced cardiac injury. Cafestol had no toxic effects and was safe at 5 mg/kg bodyweight.	
			<i>In vitro</i> (MTT and BrdU assays)	Human umbilical vein endothelial cells	Urotensin II-induced cell proliferation was reduced by treatment with 3-10 μM (18 h).	-↑ of expression of urotensin II-induced IL-8. Anti-inflammatory response mediated by phosphorylation of ERK, upstream of Nrf2. Nrf2 protein levels elevated in the nucleus lead to cafestol acetate-↑ HO-1 expression.	No cytotoxic effect at concentration of 1-10 μM.	(Tsai et al., 2018)
			<i>In vitro</i> (MTS and BrdU assay, injury, and migration analysis)	HMVECs Human microvascular endothelial cells	-↑ viability significant at 75 μM (24h), with only 5% viability at 100 μM. At 50 μM (24 h), anti-proliferative and	-↑ Active VEGFR-2 and its downstream effector Akt. ↓ release of VEGF.	↓ Cell viability in a dose-dependent manner, with (58) being more potent than (60). (58) demonstrated higher	(Moeenfarid and Alves, 2020)

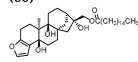
(continued on next page)

Table 1 (continued)

Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
						significant anti-migration effect reported.		proliferation $\rightarrow$ than (60).	
		Kahweol palmitate (58) 		<i>In vitro</i> (MTT, LDH, Transwell invasion and wound healing assays)	HT-1080	$\rightarrow$ Migration and invasion.	$\rightarrow$ phosphorylation of Akt, p38 MAPK, and JNK1/2 (not of ERK1/2) $\rightarrow$ NF- κ B pathway $\rightarrow$ transcription and translation of MMP9.	PMA -induced cell proliferation of HT-1080 to test for migration capacity of the cells. $\downarrow$ Proliferation in a concentration-dependent manner (1, 5, and 10 μ M).	(Choi et al., 2019)
		Kahweol acetate (59) 		<i>In vitro</i> (CCK-8 assay)	Hep3B	Significant $\rightarrow$ in a concentration-dependent manner (24 h). Pro-apoptotic and anti-proliferative effect.	Caspase-dependent Apoptosis: $\uparrow$ sub-G1 cellular population, cleaved caspase 3 and PARP $\downarrow$ expression of pSrc and $\rightarrow$ mTOR signalling pathway $\downarrow$ expression of pAkt, p-mTOR, p-P70S6K, and p-4E-BP1. $\rightarrow$ cell growth. $\rightarrow$ pSTAT3.	Morphology alterations were observed: rounded morphology, contraction, and attachment loss	(Seo et al., 2021)
				<i>In vitro</i> (CCK-8 assay)	SNU182 SNU423	Significant $\rightarrow$ in a concentration-dependent	Caspase-dependent Apoptosis:	Morphology alterations were	(Seo et al., 2021)

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vitro</i> (MTS and BrdU assay, injury, and migration analysis)	HMVECs Human microvascular endothelial cells	manner (24 h). Pro-apoptotic and anti-proliferative effect. → viability significant at 75 and 100 μM (24 h). At 50 μM (24 h), anti-proliferative reported. No effect on migration.	↑ sub-G1 cellular population, cleaved caspase 3 and PARP ↓ expression of pSrc and → mTOR signalling pathway ↓ expression of pAkt, p-mTOR, p-P70S6K, and p-4E-BP1. → cell growth. → pSTAT3. → Active VEGFR-2 and its downstream effector Akt. ↓ release of VEGF.	observed: rounded morphology, contraction, and attachment loss	(Moeenfar and Alves, 2020)
	Cafestol palmitate (60) 		<i>In vitro</i> (TUNEL assay)	PC-3	Strong cytotoxic effect, cell proliferation almost completely → (24 or 48 h).	Apoptosis: ↑ cleaved caspase-3 and PARP. ↓ Bcl-2 and Bcl-xL. → STAT3.	Combined treatment of 30 μM (59) and 30 μM (56) (CI < 1).	(Iwamoto et al., 2019)
	Co-administration of (56) and (59)		<i>In vitro</i> (TUNEL assay) <i>In vitro</i> (cell migration assay)	DU145 LNCaP PC-3	Strong cytotoxic effect, cell proliferation almost completely → (24 or 48 h). → Migration	Apoptosis: ↑ cleaved caspase-3 and PARP. ↓ Bcl-2 and Bcl-xL. → STAT3. ↓ EMT-proteins Twist, Snail and Slug. → AR in AR-positive LNCaP and LNCaP-SF. → CCL2-CCR2 and CCL5-CCR5 axes.	Combined treatment of 30 μM (59) and 30 μM (56) (CI < 1). Combined treatment of 30 μM (59) and 30 μM (56).	(Iwamoto et al., 2019) (Makino et al., 2021)
			<i>In vitro</i> (cell migration assay)	DU-145 LNCaP	→ Migration Tumour growth significantly ↓	↓ EMT-proteins Twist, Snail and Slug.	Combined treatment of 30 μM (59) and 30 μM (56).	

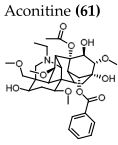
(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
			<i>In vivo</i> (DU-145 xenograft study in severe combined immunodeficient (SCID) mice)			→ AR in AR-positive LNCaP and LNCaP-SF. → CCL2-CCR2 and CCL5-CCR5 axes. Possibly same as <i>in vitro</i> .	Oral administration of (59) and (56) at 30 mg/kg.	
			<i>In vitro</i> (Cell proliferation assay, cells counted with a hemocytometer; TUNEL assay)	ACHN	Combination of 30 μM (59) and 30 μM (56) was significantly ↑ anti-proliferative than either compound alone (24 or 48 h).	Apoptosis: ↓ activation of pSTAT3, expression of Bcl-2 and Bcl-xL. ↑ expression of Bax. No cleaved caspase-3 nor cleaved PARP detected.	Dose-dependent.	
			<i>In vitro</i> (Cell migration assay)	ACHN	→ EMT and migration.	→ Akt phosphorylation → Snail and Twist expression. ↓ N-cadherin, β-catenin, CCR2, CCR4 and CCR5.	Combination of 30 μM (59) and 30 μM (56). ↓ PD-L1 (tumour microenvironment alterations)	(Makino et al., 2021)
			<i>In vitro</i> (Cell migration assay) <i>In vitro</i> (MTT assay, Hoechst33258 staining assay, Western Blot)	Caki-1 MIA PaCa-2	→ EMT and migration. ↓ 90% proliferation rates with concentrations of up to 80μM. LD ₅₀ = 20 - 40 μM	→ Akt phosphorylation → Snail and Twist expression. ↓ N-cadherin, β-catenin, CCR2, CCR4 and CCR5. → cell proliferation in a dose-dependent manner ↑ cell apoptosis in a dose dependent-manner through NF-κB signalling pathway. ↓ expression of Bax and Bcl-2	Combination of 30 μM (59) and 30 μM (56). ↓ PD-L1 (tumour microenvironment alterations)	

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
						↑ protein level of Bax in mitochondria, cytochrome C		
MACROCYCLIC	 C19-norditerpenoid alkaloid	Purchased from Sigma-Aldrich – Can be isolated from <i>Salvia</i> spp. In Africa	<i>In vitro</i> (MTT assay, Hoechst33258 staining assay, Western Blot)	PANC-1	↓ 75% proliferation rates with concentrations of up to 80μM. LD ₅₀ = 20 - 40 μM	→ cell proliferation in a dose-dependent manner ↑ cell apoptosis in a dose dependent-manner through NF-κB signalling pathway. ↓ expression of Bax and Bcl-2 ↑ protein level of Bax in mitochondria, cytochrome C ↑ cl-caspase-9 and cl-caspase-3	→ tumor growth → cell apoptosis	(Ji et al., 2016) (Du et al., 2013)
			<i>In vivo</i> (Xenograft Mouse Model)		Tumor size reduction by 20% (day 28, 10 mg/kg) in a dose-dependent manner			
			<i>In vitro</i> (cell viability assayed by WST-1 ki, Annexin-V apoptotic Assay, Western Blot)	B16	IC ₅₀ = 11.74 ± 1.53 μgM (48h)	→ cell growth ↑ apoptosis → PI3K/AKT and MAPK/ERK1/2 signalling pathways → protein levels of PCNA, ↑ cleavage of Caspase-3 → Caspase-3 and Caspase-8		
			<i>In vivo</i> (Female 6-8 weeks BALB/c nude mice)		Reduced tumor weight		→ tumor growth ↓ protein levels of PCNA ↑ cleaved Caspase-3	(Yuan et al., 2019)
			<i>In vitro</i> (MTT, Hoechst 33258, acridine orange/ethidium bromide)	HepG2	Significant → effect in a time and concentration-dependent manner. 20 mg/L for 24, 48, and 72 h ↓ colony formation	Apoptosis via p53-PUMA, PI3K-Akt, and IL-1-NFκB-IAP pathways. ↑ NF-κB signaling, HIF-1 signaling, apoptosis, cancer,	↓ genes: cell attachment, cell migration, mitosis, cell cycle, DNA replication, and	

(continued on next page)

the potential to discover promising diterpenes within the African continent.

In another study, researchers isolated different phorbol and ingenane esters from *Euphorbia grandicornis* and evaluated their effects on PKC activation and platelet stimulation. Phorbol esters are known for their ability to promote tumors, and in particular, 12-O-

tetradecanoylphorbol-13-acetate is used as a biomedical research tool in models of carcinogenesis. Compounds that caused platelet stimulation were also effective in activating PKC. This was demonstrated by the translocation of PKCs to the membrane, phosphorylation of PKC substrates and activation of PKC signalling pathways. Although the tetracyclic myrsinane type diterpene was not active, several others tested

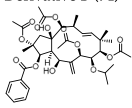
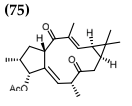
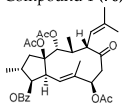
Table 1 (continued)

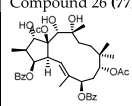
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Cembrane	 <chem>CC(C)[C@H]1C[C@@H](O)[C@H](O)[C@@H]2C[C@H](C)[C@H]1C[C@@H](C)[C@H]2</chem>	<i>Nicotiana tabacum</i> L. (sparsely branched panicles)	staining, Annexin V-FITC/PI, and Cell RNA Kit, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis		ability in HepG2 and SMMC-7721	and autophagy. ↓ adhesion, citric acid cycle, conduction pathway, MAPK signaling, TGF-β signaling, P13K-Akt signaling, and cell cycle.	growth factor binding. ↑ genes: protein localization, metal ion transition, cell death, apoptosis progression, ubiquitin transferase activity, and protein transport	(Yuan et al., 2019) (Villareal et al., 2018)
			<i>In vitro</i> (MTT, Hoechst 33258, acridine orange/ethidium bromide staining, Annexin V-FITC/PI, and Cell RNA Kit, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis <i>In vitro</i> (Western blot, MTT, among others)	SMMC-7721 HL-7702 B16	Significant ↑ effect in a time and concentration-dependent manner. 20 mg/L for 24, 48, and 72 h ↓ colony formation ability in HepG2 and SMMC-7721 No significant change in the cell after 24 h	Apoptosis via p53-PUMA, P13K-Akt, and IL-1-NFκB-IAP pathways. ↑ NF-κB signaling, HIF-1 signaling, apoptosis, cancer, and autophagy. ↓ adhesion, citric acid cycle, conduction pathway, MAPK signaling, TGF-β signaling, P13K-Akt signaling, and cell cycle. ↑ Migration, invasion, and cell adhesion (↑ Egr1; ↓ Id2, Sytl2, Mitf genes expression)	↓ genes: cell attachment, cell migration, mitosis, cell cycle, DNA replication, and growth factor binding. ↑ genes: protein localization, metal ion transition, cell death, apoptosis progression, ubiquitin transferase activity, and protein transport	

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Daphnane	Gnidilatin (63) <chem>CC(C)[C@H]1C[C@@H](O)[C@H](O)[C@@H]2C[C@H](C)[C@H]1C[C@@H](C)[C@H]2</chem>	<i>Thymelaea hirsuta</i> Endl. (leaves)	<i>In vivo</i> (tumorigenesis assays) <i>In vitro</i> (fluorescent analysis, western blot, RT-PCR)	Male C57BL/6 J mice HTB-37	↓ tumour colonization Cell proliferation by 25.33 % ± 9.71 at 1.6 μM.	↓ tumour colonization → ↓ CD44, MMP2, MMP9 ↓ Ki-67 ↓ Cell growth (G1 phase) ↓ GSK3β and Akt Cytostatic accompanied by epithelial morphogenesis (↑ ITGA2 and MUC2)	Patient tolerated the treatment well and has remained remission free for 18 months	(Villareal et al., 2018) (Trinel et al., 2020)
	Huratoxin (66) <chem>CC(C)[C@H]1C[C@@H](O)[C@H](O)[C@@H]2C[C@H](C)[C@H]1C[C@@H](C)[C@H]2</chem>	<i>Hura crepitans</i> L. (latex)	Clinical trial (superficial basal cell carcinoma)		0.05 % gel applied on two consecutive days.			
Ingenane	Ingenol mebutate (67) <chem>CC(C)[C@H]1C[C@@H](O)[C@H](O)[C@@H]2C[C@H](C)[C@H]1C[C@@H](C)[C@H]2</chem>	<i>Euphorbia peplus</i> L. (sap)	<i>In vitro</i> (MTT assay)	Caov-4	IC ₅₀ = 46.27 ± 3.86 μM (48 h)	↑ total apoptosis (late and early). ↑ ROS production. ↓ MMP → caspase 3/9.		(Bahmani et al., 2017; Ghanadian et al., 2015)
Jatrophane	Derivative A (73) <chem>CC(C)[C@H]1C[C@@H](O)[C@H](O)[C@@H]2C[C@H](C)[C@H]1C[C@@H](C)[C@H]2</chem>	<i>Euphorbia osyridea</i> Bioss. (aerial flowering parts)	<i>In vitro</i> (MTT assay) <i>In vitro</i> (Luminescent Cell Viability Assay kit)	OVCAR-3 Caov-4	IC ₅₀ = 38.81 ± 3.30 μM (48 h) IC ₅₀ = 36.48 ± 3.18 μM (48 h)	↑ total apoptosis (late and early). ↑ ROS production. ↓ MMP → caspase 3/9.	Not cytotoxic in normal human cells (>100 μM)	(Bahmani et al., 2017; Ghanadian et al., 2015) (Ling et al., 2019)

(continued on next page)

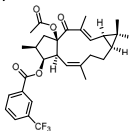
Table 1 (continued)

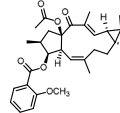
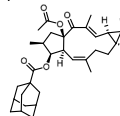
Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Derivative B (74) 		(G7570, Promega), AnnexinV-FITC, PI, or DAPI, ApoTox-Glo Triplex and TMRM assay)	OVCAR-3 ALL (KOPN-8)	IC ₅₀ = 42.59 ± 4.50 µM (48 h) IC ₅₀ = 1–10 µM (48 h)	Selective mitochondrial ROS production. → mitophagy ↓ MMP. → cell cycle arrest at the G2/M stage. → caspase (3/7), and cleavage of PARP-1.		
	Jatrogossone A (75) 	<i>Jatropha gossypifolia</i> L. (whole plant)	<i>In vitro</i> (Luminescent Cell Viability Assay kit (G7570, Promega), AnnexinV-FITC, PI, or DAPI, ApoTox-Glo Triplex and TMRM assay) <i>In vitro</i> (MTT, Griess assay and ELISA)	ALL (SEM) ALL (UoC-B1) BCR-ABL-WT, BCR-ABLDKO MDA-MB-231, SUM149, and U2OS LPS stimulated RAW 264.7 cells.	IC ₅₀ = 1–10 µM (48 h) IC ₅₀ = >10 µM (48 h) IC ₅₀ = 7.4 ± 0.6 µM (24 h)	Selective mitochondrial ROS production. → mitophagy ↓ MMP. → cell cycle arrest at the G2/M stage. → caspase (3/7), and cleavage of PARP-1. → initial phase of the inflammatory cascade initiated by LPS, through regulation of the NF-κB signalling pathway: → translocation of the p65 subunit, secretions of IL-6 and TNF-α.	Not cytotoxic in normal human cells (>100 µM) Third member discovered of a rare class of <i>Euphorbia</i> diterpenes with a rare 5/10 fused ring system.	(Ling et al., 2019) (Su et al., 2019)
	Compound 1 (76) 	<i>Euphorbia helioscopia</i> L. (aerial parts)	<i>In vitro</i> (Rho123 accumulation, MTT, MDR reversal assay)	HepG2/ADR	Sensitivity reversal IC ₅₀ (Pgp inhibitor+ADR) = 1.09 ± 0.24 µM Intrinsic cytotoxicity IC ₅₀ = >150 µM RF = 71 (48 h)	P-glycoprotein (Pgp)-dependent MDR modulation.	RF = IC ₅₀ (ADR) / IC ₅₀ (Pgp inhibitor+ADR). Metabolically stable. Greater chemoreversability than tariquidar. SAR studies results indicate enhanced	(Zhu et al., 2016)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Compound 26 (77) 	<i>Pedilanthus tithymaloides</i> (L.) Poit. (leaves and stems)	<i>In vitro</i> (Rho123 accumulation, MTT, MDR reversal assay) <i>In vivo</i> (xenografts in female BALB/c nude mice (5 weeks old))	HLF HepG2/ADR	IC ₅₀ = >100 µM (48 h) Coadministration with ADR. <u>Tumour volume (mean):</u> Treated = 44.88 mm ³ . Control = 144.48 mm ³ . <u>Excised tumour weight (mean):</u> Treated = 0.0209 g. Control group = 0.0563 g. (21 days)	P-glycoprotein (Pgp)-dependent MDR modulation. P-gp-dependent MDR modulation.	activity through presence of a saturated A ring, increased lipophilicity, and alterations in the C2/C5 region. RF = IC ₅₀ (ADR) / IC ₅₀ (Pgp inhibitor+ADR). Metabolically stable. Greater chemoreversability than tariquidar. SAR studies results indicate enhanced activity through presence of a saturated A ring, increased lipophilicity, and alterations in the C2/C5 region. ADR (5 mg/kg) with or without the jatrophane (10 mg/kg). Inhibition rate of 62.89%. Coadministration extended overall survival rate of the mice.	(Zhu et al., 2016) (Reis et al., 2013, 2014)

(continued on next page)

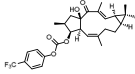
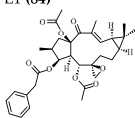
Table 1 (continued)

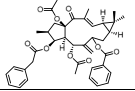
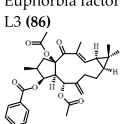
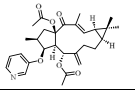
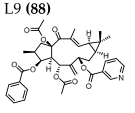
Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Lathyrane				<i>In vitro</i> (MTT assay)	L5178Y – PAR	IC ₅₀ = 43.99 ± 3.67 μM (72 h)	↓P-gp efflux activity	Ability to target different cellular contexts with concomitant high antiproliferative activity. P-gp modulation Resensitizes multidrug resistant phenotypes	
		<i>Euphorbia piscatoria</i> Aiton (aerial parts)	<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTT assay)	L5178Y – MDR	IC ₅₀ = 52.60 ± 3.84 μM (72 h)	↓P-gp efflux activity	Ability to target different cellular contexts with concomitant high antiproliferative activity. P-gp modulation Resensitizes multidrug resistant phenotypes Strong modulation of P-gp efflux activity. Reverses P-gp-Mediated MDR Improved the cytotoxicity of doxorubicin synergistically (CI = 0.09)	(Reis et al., 2013, 2014) (Reis et al., 2017)	
				EPG85-257	IC ₅₀ = 9.15 ± 2.44 μM (72 h)	↓P-gp efflux activity			
				EPP85-181P	IC ₅₀ = 17.76 ± 5.65 μM (72 h)				
				HT-29	IC ₅₀ = 9.32 ± 2.33 μM (72 h)				
				EPG85-257RN	IC ₅₀ = 3.58 ± 1.93 μM (72 h)				
				EPP85-181RN	IC ₅₀ = 10.11 ± 6.65 μM (72 h)				
				HT-29RN	IC ₅₀ = 3.82 ± 1.08 μM (72 h)				
				EPG85-257RD	IC ₅₀ = 3.22 ± 0.70 μM (72 h)				
				EPP85-181RD	IC ₅₀ = 11.34 ± 4.07 μM (72 h)				
				HT-29RD	IC ₅₀ = 9.67 ± 2.77 μM (72 h)				
				L5178Y-PAR	IC ₅₀ = 19.73 ± 1.34 μM (72 h)				

Class		Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
		Jolkinolate P (81) 		<i>In vitro</i> (MTT assay)	L5178Y_M DR	IC ₅₀ = 24.17 ± 3.40 μM (72 h)	↓P-gp efflux activity ↓P-gp efflux activity ↑caspase 3	Strong modulation of P-gp efflux activity. Reverses P-gp-Mediated MDR Improved the cytotoxicity of doxorubicin synergistically (CI = 0.09) Selective apoptosis induction in resistant pancreatic cells. → caspase mediated apoptosis	(Reis et al., 2017) (Teng et al., 2018)
		<i>In vitro</i> (MTT assay)		L5178Y-PAR	IC ₅₀ = 24.71 ± 5.52 μM (72 h)				
		Jolkinolate U (82) 		<i>In vitro</i> (MTT assay)	L5178Y_M DR	IC ₅₀ = 30.87 ± 3.68 μM (72 h)	↓P-gp efflux activity ↑caspase 3 ↓P-gp efflux activity ↑caspase 3	Selective apoptosis induction in resistant pancreatic cells. → caspase mediated apoptosis MDR selective antiproliferative effect Selective apoptosis → in resistant gastric cells. → caspase-mediated apoptosis. Improved the cytotoxicity of doxorubicin synergistically (CI = 0.5)	
		<i>In vitro</i> (MTT assay)		EPG85-257	IC ₅₀ = 5.77 ± 0.28 μM (72 h)				
		EPP85-181		IC ₅₀ = 8.61 ± 0.58 μM (72 h)					
		EPG85-257RN		IC ₅₀ = 4.45 ± 0.93 μM (72 h)					
		EPP85-181RDB		IC ₅₀ = 5.89 ± 0.07 μM (72 h)					
		EPP85-181RN		IC ₅₀ = 6.63 ± 0.95 μM (72 h)					
		EPG85-257RBD		IC ₅₀ = 4.39 ± 1.01 μM (72 h)					
		L5178Y-PAR		IC ₅₀ = 49.51 ± 6.03 μM (72 h)					

(continued on next page)

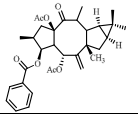
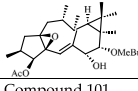
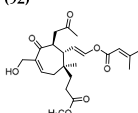
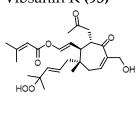
Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Jolkinolate B (83) 		<i>In vitro</i> (MTT assay) <i>In vitro</i> (Sulforhodamine B colorimetric assay)	L5178Y_MDR EPG85-257 EPP85-181 EPG85-257RD EPG85-257RN EPP85-181RD EPP85-181RN A549	IC ₅₀ = 54.09 ± 2.68 μM (72 h) IC ₅₀ = 6.24 ± 1.08 μM (72 h) IC ₅₀ > 30 μM (72 h) IC ₅₀ = 2.34 ± 0.67 μM (72 h) IC ₅₀ = 5.55 ± 0.88 μM (72 h) IC ₅₀ = 2.52 ± 1.44 μM (72 h) IC ₅₀ > 30 μM (72 h) IC ₅₀ = >40 μM (72 h)	JP-gp efflux activity ↑caspase 3 Compounds L3 and L9 (target the same protein required for the G1 to S transition) disrupted normal cell cycle progression, whereas compounds L2, L3, L8 and L9 → obvious actin filament aggregation, as well as partial interference of the microtubule network, resulting in F-actin aggregation.	MDR selective antiproliferative effect Selective apoptosis → in resistant gastric cells. → caspase-mediated apoptosis. Improved the cytotoxicity of doxorubicin synergistically (CI = 0.5) L2 exerts collateral sensitivity towards MDR cells. This work is the first report of a Euphorbia factor with collateral sensitivity activity.	
	Euphorbia factor L1 (84) 	<i>Euphorbia lathyris</i> L. (seeds)	<i>In vitro</i> (Sulforhodamine B colorimetric assay) <i>In vitro</i> (MTT assay)	MDA-MB-231 KB KB-VIN MCF-7 A549 MDA-MB-231 KB KB-VIN	IC ₅₀ = >40 μM (72 h) IC ₅₀ = >40 μM (72 h) IC ₅₀ = >40 μM (72 h) IC ₅₀ = >40 μM (72 h) IC ₅₀ = >40 μM (72 h) IC ₅₀ = >40 μM (72 h) IC ₅₀ = 33.2 ± 7.7 μM (72 h) IC ₅₀ = 7.2 ± 1.5 μM (72 h)	Compounds L3 and L9 (target the same protein required for the G1 to S transition) disrupted normal cell cycle progression, whereas compounds L2, L3, L8 and L9 → obvious actin filament aggregation, as well as partial interference of the microtubule network,	L2 exerts collateral sensitivity towards MDR cells. This work is the first report of a Euphorbia factor with collateral sensitivity activity. At 20 μM of <i>Euphorbia</i> 's compound, they were able to reverse MDR	(Teng et al., 2018) (Yang et al., 2020)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
	Euphorbia factor L2 (85) 			MCF-7 A549	IC ₅₀ = >40 μM (72 h) IC ₅₀ = 14.6 ± 0.1 μM (72 h)	resulting in F-actin aggregation.	of HepG2/ADR cells to ADR, more potent activity than positive control Verapamil.	
	Euphorbia factor L3 (86) 			MDA-MB-231 KB KB-VIN MCF-7 A549	IC ₅₀ = 31.6 ± 2.3 μM (72 h) IC ₅₀ = 7.9 ± 0.3 μM (72 h) IC ₅₀ = 8.0 ± 1.3 μM (72 h) IC ₅₀ = 25.9 ± 4.3 μM (72 h) IC ₅₀ = 11.8 ± 1.8 μM (72 h)			
	Euphorbia factor L8 (87) 			MDA-MB-231 KB KB-VIN MCF-7 A549	IC ₅₀ = 24.4 ± 4.0 μM (72 h) IC ₅₀ = 17.7 ± 1.2 μM (72 h) IC ₅₀ = 16.9 ± 2.9 μM (72 h) IC ₅₀ = 23.8 ± 4.7 μM (72 h) IC ₅₀ = 6.7 ± 0.5 μM (72 h)			
	Euphorbia factor L9 (88) 			MDA-MB-231 KB KB-VIN MCF-7 HepG2/ADR	IC ₅₀ = 21.9 ± 1.3 μM (72 h) IC ₅₀ = 6.1 ± 0.2 μM (72 h) IC ₅₀ = 5.7 ± 0.1 μM (72 h) IC ₅₀ = 8.4 ± 1.4 μM (72 h) IC ₅₀ = >100.00 μM (48 h)			

(continued on next page)

Table 1 (continued)

Class	Name and structure	Origin Plant (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
Visbane	Euphorbia Factor L15 (89) 		<i>In vitro</i> (MTT assay) <i>In vitro</i> (MTT assay)	HepG2/AD R A549	IC ₅₀ = >100.00 µM (4 h)	Apoptosis → mitochondrial dysfunction ↑ Intracellular ROS levels		(J. Lu et al., 2014)
	Compound 84 (90) 				IC ₅₀ = 1.11 µM (48h)			(Li et al., 2022)
	Compound 101 (92) 	<i>Viburnum odoratissimu</i> m (leaves)	<i>In vitro</i> (MTS assay)	HL-60	IC ₅₀ = 16.40 ± 0.12 µM (48h)	HSP90 →		(Zhu et al., 2018)
	Vibsanin K (93) 	<i>Viburnum odoratissimu</i> m (leaves and twigs)	<i>In vitro</i> (HSP90 dependent luciferase refolding assay) <i>In vivo</i> (xenograft model in mice)	Hep3B cells	IC ₅₀ = of 19.16 µM 100 mg/kg or 200 mg/kg notably reduced tumor volumes and weights compared with the control group	HSP90 → Apoptosis → PI3K/AKT Mitochondrial damage and oxidative stress		(Zhu et al., 2018) (Xue et al., 2023)
	Ethyl acetate extract (5-epi-vibsanin H, 5-epi-Methylvibsanin H, 15-O-Methylvibsanin H, vibsanin B, vibsanin Q, vibsanin D and vibsanin C)	<i>Viburnum odoratissimu</i> m (leaves)						

SKOV-3 - Human ovarian cancer cells; **MDA-231**, **MDA-MB435**, **MCF-7**, **T47D**, **BT549** - Human breast cancer cells; **HCT116** and **SW480** - Human colon cancer cells; **U251**, **U87-MG** - human glioblastoma cell line; **CaSki**, **SiHa** - Human cervical cancer cell lines; **MHCC97-H** and **Bel7402** - Human liver cancer cell lines; **SKBR-3** and **BT474** - ERBB2+ Human Breast Cancer cell lines; **B16F10** and **C57BL/6** - Murine Melanoma cell line; **PANC-1**, **MIA PaCa-2** - Human Pancreas cancer cell lines; **AGS** and **MKN-45** - Human Gastric cancer cell lines; **KYSE-150** - Human esophageal squamous cell carcinoma cell line; **H1299** and **H1975** - Human non-small-cell lung cancer cells. **PBMC** - Peripheral-blood mononuclear cells; **BAEC** - Bovine Aorta Endothelial Cells; **HUVEC** - Human umbilical vein endothelial cells; **HL-60** - Human promyelocytic leukemia cell line; **HT-1080** - Human fibrosarcoma cell line; **L5178Y** - **PAR** - Parental Mouse T lymphoma cell line; **L5178Y** - **MDR** - Mouse T lymphoma cell line transfected with the human MDR1 gene; **EPG85-257** - Human gastric cancer cell line; **EPP85-181** - Human pancreatic cancer cell line; **HT-29**, **Colo205**, **Colo320** - Human Colon Cancer cell line; **EPG85-257RN** - Human gastric cancer cell line resistant to mitoxantrone; **EPG85-257RD** - Human gastric cancer cell line resistant to daunorubicin; **EPP85-181RN** - Human pancreatic cancer cell line resistant to mitoxantrone; **EPP85-181RD** - Human pancreatic cancer cell line resistant to daunorubicin; **HT-29RN** - Human colon cancer cell line resistant to mitoxantrone; **HT-29RD** - Human colon cancer cell line resistant to daunorubicin. **4E-BP1** - Eukaryotic translation initiation factor 4E-binding protein 1; **786-O** and **A-498** - Human ccRCC cell lines; **A375**, **B16** - melanoma cancer cell line; **A4** -?; **A549** - human non-small cell lung cancer cells; **A427** - Lung carcinoma cell line; **A431** - Epidermoid carcinoma; **ABCB1** - ATP-binding cassette sub-family B member 1, P-gp gene encoder; **ACHN** and **Caki-1** - Human renal cancer cells; **ADR** - Adriamycin; **AGS**, **MKN-28**, **SNU-216**, **SNU-601**, **SNU-668**, and **YCC** - Human gastric cancer cell lines; **Akt** - Protein kinase B; **ALL** - Acute lymphoblastic leukaemia cells (KOPN-8, SEM, and UoC-B1); **AML12** - Mouse hepatocyte cell line; **AMPKα** - AMP-activated protein kinase α; **ANDRO** - Andrographolide; **AO/EB** - Acridine orange and ethidium bromide; **AP-2** - Activator protein-2; **Ara-C** - cytosine arabinoside; **ARPE-19** - Normal human retinal pigment epithelial cells; **ASK1** - Apoptosis signal-regulating kinase 1; **ATF-2** - Activating transcription factor-2; **ATF3** - Activating transcription factor 3; **Atg** - Autophagy related-proteins; **ATM** - Ataxia-telangiectasia mutated serine/threonine kinase; **ATP** - Adenosine triphosphate; **Bak1** - Bcl-2 homologous antagonist killer; **Bax** - Bcl-2-like protein 4; **Bcl-2** - B-cell lymphoma 2 protein; **BCR-ABL-WT**, **BCR-ABLDKO** - Murine cell models; **BrdU** - Bromodeoxyuridine; **BV-2** - microglial cells derived from C57/BL6 murine; **C57BL/6** - Primary Hepatocytes; **C6** - Rat glioma cell line; **Caov-4**, **OVCAR-4**, **OVCAR-8**, and **OVCAR-3** - Ovarian cancer cells; **CAT** - Catalase; **CC50** - Cytotoxic concentration for 50% of cells; **CCAR1** - Cell Division Cycle And Apoptosis Regulator 1 protein coding gene; **CCK** - Cell Counting Kit; **CCL** - chemokine ligand; **CCND1** - CCND1 gene encodes the cyclin D1 protein; **CCR** - chemokine receptor; **ccRCC** - Clear cell renal cell carcinoma; **cdc25c** - M-phase inducer phosphatase 3; **CDK1**, **cdc2** - cyclin-dependent kinase 1; **CEM** - Leukaemia cell line; **cFLIP** - Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; **CHK2** - Protein encoded by the CHEK2 (Checkpoint kinase 2), a tumor suppressor gene; **CHOP** - C/EBP Homologous Protein; **CRC** - Colorectal carcinoma; **CREB** - cAMP response element-binding protein; **COX-2** - Cyclooxygenase-2; **CPT** - Cryptotanshinone; **CREB2** - cAMP response element-binding protein 2; **Cyr61** - Cysteine-rich angiogenic inducer 61; **DcR** - Decoy receptor; **DHA** - Dehydroabietic Acid; **DHCR24** - 24-dehydrocholesterol reductase, crucial enzyme of cholesterol biosynthetic pathway, is involved in lipid rafts formation, related with HCC; **DNA** - Deoxyribonucleic acid; **DOX** - Doxorubicin; **DR5** - Death receptor 5; **Dvl 2** - Segment polarity protein dishevelled homolog; **EBV** - Epstein Barr Virus; **EC109** - human oesophageal cancer cell line; **ECM** - Extracellular matrix; **Egr1** - Early growth response protein 1; **eIF2α** - Eukaryotic translation initiation factor 2A; **EKA** - Ent-kaur-16-en-18-oic acid; **EMT** - Epithelial-to-mesenchymal transition; **EPG85-257P** - Parental gastric cancer cells; **EPG85-257RDB** - Gastric human cancer cells resistant to RDB; **EPG85-257RNOV** - Gastric human cancer cells resistant to mitoxantrone; **EPP85-181P** - Parental pancreatic carcinoma cells; **EPP85-181RDB** - Pancreatic human cancer cells resistant to RDB; **EPP85-181RN** - Pancreatic human cancer cells resistant to RN; **EPP85-181RNOV** - Pancreatic cancer cells selected against mitoxantrone; **ER** - Oestrogen; **ERK** - Extracellular signal-regulated kinase; **EZH2** - Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit; **FaDu** - Human pharynx squamous cancer cells; **FAK** - Focal adhesion kinase; **FASN** - Fatty acid synthase; **FITC** - Fluorescein IsoTioCyanate; **FLIC** - FLICE-like inhibitory protein; **FSK** - Forskolin; **GES-1** - human gastric epithelial cells; **GFA** -

Grandiflorenic Acid; **GI₅₀** - Concentration of the agent that inhibits growth by 50%; **Glc** - Glucose-starved conditions; **Glc** + General culture conditions; **GM-CSF** - Granulocyte-macrophage colony-stimulating factor; **GSK3 β** - Glycogen synthase kinase 3 β ; **GPx-1** - Glutathione peroxidase; **GSH** - Glutathione; **GSK 3 β** - Glycogen synthase kinase-3 beta; **GST** - Glutathione S-Transferases; **H1299** - Non-small cell lung cancer line **H184B5F5/M10** - human mammary epithelial cells; **H2A.X** - Histone H2AX; **HAT** - Histone Acetyltransferase; **HCC** - Hepatocellular carcinoma; **HCT-8**, **HCT-116**, **SW480**, **LoVo**, **Caco-2** and **HT-29** - human colorectal carcinoma cell line; **HLCA** - 15-Hydroxy-8(17),13(E)-labdadiene-19-carboxylic acid; **HDAC** - Histone deacetylase; **HEC-1-A**, **HEC-1-B**, and **KLE** - Endometrial cell lines; **HEK293** - Human embryonic kidney 293 cell line; **HeLa**, **KB** - cervical cancer cells; **Hep3B**, **SNU182**, and **SNU423** - Human hepatocellular carcinoma cells; **HepG2/ADR** - Adriamycin resistant human hepatocellular carcinoma cells; **HER-2** - human epidermal growth factor receptor 2; **HGT-1**, **SNU-1**, **SNU-6**, and **NCI-N87** - human gastric cancer cell lines; **HEI-OC1 cells** - Auditory cell line derived from the mouse organ of Corti and cochlear explants of C57BL/6J mice; **HL 7702** - normal human liver cells; **HLF** - Normal Human Lung Fibroblasts Cells; **HMVECs** - Human microvascular endothelial cells; **HO-1** - Heme oxygenase 1; **HOE** - normal human ovarian surface epithelial; **HOTAIR** - HOX transcript antisense RNA gene; **Hs 738.St/Int** - normal gastric human cells; **HSP** - Heat Shock Protein; **HT-1080** - Human fibrosarcoma cells; **HTB-37** - Human colon adenocarcinoma cell line Caco-2; **HPV** - human papillomavirus; **HuH7.5** - Liver cancer cell line; **HUVECs** - Human Umbilical Vein Endothelial Cells; **IBD** - Inflammatory Bowel Disease; **Id2** - DNA-binding protein inhibitor ID-2; **IL** - Interleukin; **IkB α** - NF-kappa-B inhibitor alpha; **INF γ** - Interferon- γ ; **iNOS** - inducible nitric oxide synthase; **ITGA2** - integrin subunit alpha 2; **J774A.1**, **LLCMK2**, **AMJ2-C11**, and **THP-1** - Murine macrophage cell lines; **JNK** - c-Jun N-terminal kinase; **K562** - NK-sensitive myelogenous leukaemia cell line; **KA** - Kaurenoic Acid; **KC** - Primary Kupffer Cells; **Keap1** - Kelch-like ECH-associated protein 1; **KG1**, **HL60**, **NB4**, **K562** and **CCRF-CEM** - Leukaemia cells; **KHYG-1** - NK leukaemia cell line; **Ki-67** - marker of proliferation Ki-67; **L5178Y-MDR** - MDR1 transfected L5178Y mouse T-lymphoma cells; **L5178Y-PAR**, **L5178Y-MDR** - Parental L5178Y mouse T-lymphoma cells (normal and resistant); **LC3** - Light chain 3; **LDH** - lactate dehydrogenase; **LLC** - Lewis Lung Cancer; **LNCaP** - androgen-sensitive human prostate cancer cell line; **LNCaP-SF** - androgen-independent prostate cancer cell line; **LPS** - Lipopolysaccharide; **MAPK** - Mitogen-activated protein kinases; **MCF-10A** - Non-tumorigenic breast epithelial cells; **MCF10A**, **BT549**, and **MDA-MB-231** - HER2- negative breast cancer cell lines; **MCF-7** - breast cancer DOX-sensitive cell line; **MCF-7/ADR** - Breast cancer DOX-selected derivative P-gp overexpressing; **MDA** - Malondialdehyde, **SUM149**, and **U2OS** - Solid tumour cell models; **MDM2** - Mouse double minute 2 homolog or E3 ubiquitin-protein ligase; **MDR** - Multidrug resistant; **MEK** - Mitogen-activated protein kinase kinase; **MGC-803** - human stomach cancer cell line; **MIA PaCa-2** - Human pancreatic carcinoma; **Mitf** - Microphthalmia-associated transcription factor; **MKK4** - Mitogen-Activated Protein Kinase Kinase 4; **MMP** - Mitochondrial membrane potential; **MMP2** or **MMP9** - Matrix metalloproteinase 2 or 9; **miR-21** - microRNA 21; **MM.1S** - Lymphoma cell line; **MMP** - Mitochondrial Membrane Potential; **MTT** - 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **mTOR** - mammalian target of rapamycin; **MUC2** - Mucin-2, integrin subunit alpha 2; **MYC** - MYC proto-oncogene, bHLH transcription factor; **N18** - Mouse neuroblastoma cell lines; **NCI-H1795**, **NCI-H460** - Lung carcinoma cell line; **NCI-H460/R** - Lung carcinoma resistant cell line; **ND** - No data; **NDM** - Nutrient-Deprived Medium; **NF- κ B** - Nuclear factor kappa-light-chain-enhancer of activated B cells; **NHE1** - Na⁺/H⁺ exchanger isoform 1; **NK** - Natural killer; **NO** - nitric oxide; **Nrf2** - nuclear factor erythroid 2-related factor 2; **OECM1** - Human gingival squamous carcinoma cell line; **p** - phospho; **P3HR-1** - Burkitt lymphoma cells; **p16** - p16INK4a, cyclin-dependent kinase inhibitor 2A; **p21** - p21Cip1 (alternatively p21Waf1), also known as cyclin-dependent kinase inhibitor 1 or CDK-interacting protein 1; **p27** - Cyclin dependent kinase inhibitor p27; **p38** - p38 mitogen-activated protein kinases; **p53**, **TP53** - tumor protein p53; **p65** - nuclear factor NF-kappa-B p65 subunit; **P70S6K** - Ribosomal protein S6 kinase beta-1; **PANC-1** pancreatic adenocarcinoma; **PA-NP** - polyalthic acid-containing nanoparticles; **PARP** - Poly (ADP-ribose) polymerase; **PC-3**, **DU145**, and **LNCaP** - Human prostate cancer cells; **PC₅₀** - Preferential cytotoxicity at which 50% of cancer cells are preferentially killed in NDM; **PEA3** - polyomavirus enhancer activator 3; **PERK** - Protein Kinase RNA-Like ER Kinase; **P-gp** - P-glycoprotein; **PI** - Propidium Iodide; **PI3K** - Phosphoinositide 3-kinases; **PMA** - Phorbol 12-myristate 13-acetate; **PTEN** - Phosphatase and tensin homolog; **PTX** - Paclitaxel; **RDB** - Daunorubicin; **Raf** - RAF serine/threonine kinase; **RF** - Reversal fold; **Rho** - Rhodamine; **RN** - Novantrone; **RNF6** - Ring Finger Protein 6; **ROS** - Reactive oxygen species; **RR** - Relative resistance; **SAPK** - stress-activated protein kinases; **SAS**, **SCC-9** - human oral squamous cell carcinoma; **SI** - Selectivity index; **SKBR3** and **MDA-MB-453** - HER2-positive (overexpressing) breast cancer cell lines; **Skp2** - S-phase kinase-associated protein-2; **SF295** - Glioblastoma cell line; **SGC-7901** - Human gastric cancer cell line; **SGC-7901/5-FU** - Human gastric cancer 5-Fluorouracil resistant cell line; **SMG1** - Nonsense Mediated mRNA Decay Associated PI3K Related Kinase; **SOD** - Superoxide dismutase; **Sp1** - Transcription factor Sp1; **SRB** - Sulforhodamine B; **STAT3** - Signal transducer and activator of transcription 3; **Syt12** - Synaptotagmin-Like Protein 2; **T24** - human bladder cancer cells; **TBE** - trypan blue dye exclusion; **t-Bid** - BH3-only protein BID; **TE-1** - human oesophageal cancer cell line; **TIMP-1** - metalloproteinase inhibitor 1; **TMX** - Tamoxifen; **TNF- α** - Tumor necrosis factor α ; **TUNEL** - Terminal deoxynucleotidyl transferase dUTP nick end labelling; **U87**, **A172**, **U118**, **U373**, **H4** - Glioblastoma cell lines; **U343** - Glioma cell line; **VEGF** - Vascular endothelial growth factor; **VEGFR-2** - Vascular endothelial growth factor receptor 2; **VIN** - Vincristine; **WST-8** - water-soluble tetrazolium salt; **XIAP** - X-linked inhibitor of apoptosis protein; **XTT** - 2,3-bis-(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide; **YHL-14** - Yuanhuacine.

CDK: Cyclindependent Kinase; ERBB2+: ERBB2 overexpressing; mTOR: Mammalian target of rapamycin; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol-3 kinase; SQTM1/p62: p62 protein, also called sequestosome 1; HsFPPS - Human farnesyl pyrophosphate synthase, *Homo sapiens* FPPS; MAPK - Mitogen-activated protein kinase; NLRP3 - NLR Family Pyrin Domain Containing 3; SREBF1 - Sterol Regulatory Element-Binding Transcription Factor 1.

↓: Downregulation or decrease; ↑: Upregulation or increase; ⊖: inhibition or suppression; → induction, activation, or promotion.

phorbol/ingenane esters that had a positive role in platelet activation. The study suggests that platelets are a useful model for studying PKC activators of natural origin or their chemical derivatives (Tsay et al., 2020) (Fig. 16).

Jatrophane

Jatrophane diterpenes are a large group of polyoxygenated stereochemically complex macrocyclic *Euphorbia* diterpenes. Due to their highly functionalized trans-bicyclo[10.3.0]pentadecane framework and 5/12- membered carbon ring system, they present high conformational flexibility (Su et al., 2019). Several SAR studies have been carried out to date to try to elucidate what structures are responsible for the jatrophane's biological activity. Zhu et al. (2016) reported, notably, for the first time that a saturated ring A is essential for activity, while the presence of free hydroxyl groups at the C1-C15-C14-C13 fragment has minimal influence. Furthermore, the formation of a rare C5-O-C13 bridge was found to enhance activity, while Δ 12 epoxidation negatively impacted it (Zhu et al., 2016). Generally, high flexibility of the 12-membered ring (Reis et al., 2016) lipophilicity (Zhu et al., 2016) and substitutions at the fragment C-2/C-5 are determinant of the

compounds' biological activity (Bahmani et al., 2017; Corea et al., 2004; Hu et al., 2018). The Euphorbiaceae family is known to produce a variety of jatrophane diterpenes, that, along with their polycyclic rearranged derivatives, have recently gained attention as valuable bio-resources with diverse chemical structures. They act as modulators of P-gp, effectively reversing MDR, exhibit moderate proapoptotic cytotoxicity against various cancer cells, show promise as synergistic agents when combined with anticancer drugs and enhance their anticancer activity on resistant cells (Bahmani et al., 2017; Fattahian et al., 2020; Hu et al., 2018; Ling et al., 2019; Reis et al., 2016). Nevertheless, none of the inhibitors are presently available as clinical agents because they exhibit inherent side effects, including high intrinsic toxicity, low affinity, lack of selectivity, 'off-target effects', adverse drug interactions and unpredictable pharmacokinetic interactions (Callaghan et al., 2014; Hu et al., 2018; Reis et al., 2016). This has driven the quest for safe MDR-reversal agents.

Several Euphorbiaceae family jatrophanes demonstrated MDR-selective antiproliferative activity, acting as P-gp efflux modulators (Hu et al., 2018; Reis et al., 2016, 2014). Moreover, the nature of the interaction of several jatrophanes with P-gp was studied through their

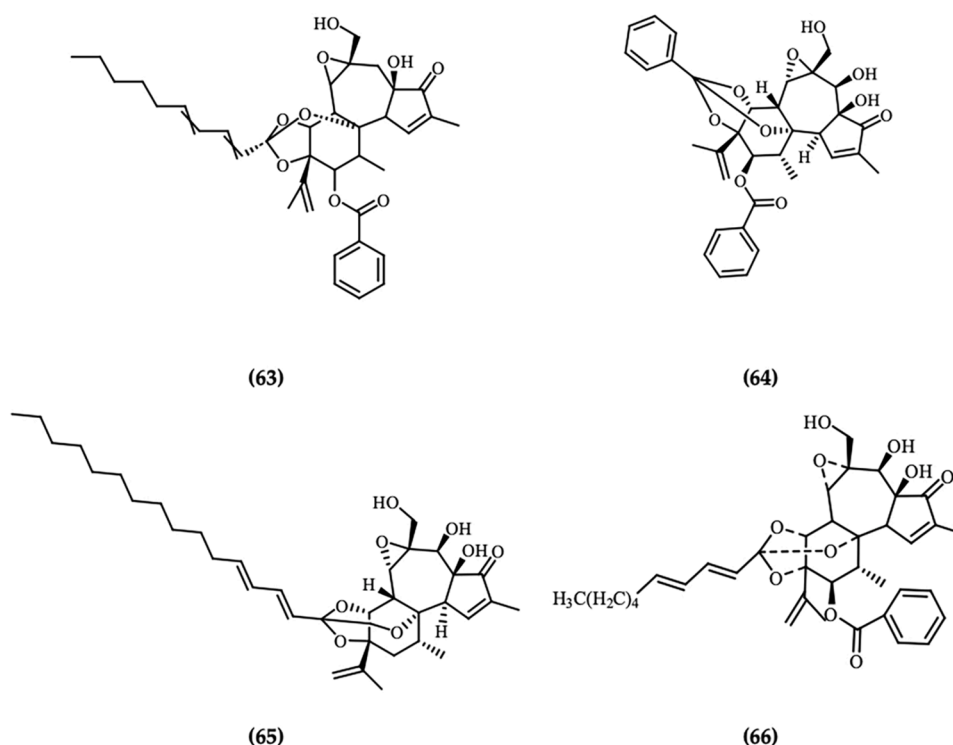


Fig. 15. Chemical structures of daphnane diterpenes gnidilatidin (63), genkwadaphnin (64), huratoxin (65) and yuanhuacine (66).

effect on the P-gp-ATPase activity. Interestingly, different jatrophanes had different effects on ATPase activity (Hu et al., 2018; Reis et al., 2016). For example, diterpene epoxywelwitschene (69) from *Euphorbia paniculata* subsp. *welwitschii* (Boiss. & Reut.) interacted with the P-gp transporter and exhibit a reduction in the transport of a second substrate. On the other hand, the jatropane euphosorophane A (70) from the fructus of *Euphorbia sororia* A. Schrenk stimulated P-gp-ATPase activity and cause the dose-dependent inhibition of doxorubicin (DOX) transport activity. Notably, the research group elucidated that (70) works probably as a competitive inhibitor to DOX in the binding site of P-gp with higher affinity than clinically available verapamil for the DOX recognition site on P-gp (Hu et al., 2018). Regarding DOX, Reis et al. (2016) also demonstrated the potential of diterpenes (69), welwitschene (71) and esulatin M (72) from *E. welwitschii* against MDR by synergistically interacting with DOX (combination index < 0.7) (Reis et al., 2016).

Despite extensive efforts in studying potent P-gp reversal agents, no P-gp modulator is presently being used in clinical practice. A novel strategy to overcome some of the issues regarding P-gp modulation, such as simultaneous inhibition of P-gp and cytochrome enzyme P450 (CYP3A4 isoform) and simultaneous modulation/inhibition in normal

and cancer cells, might be the use of collateral sensitivity. Collateral sensitivity is a phenomenon where resistance to one agent confers increased sensitivity to another agent. Reis et al. (2016) reported that (69) and (72) demonstrated selective activity against the MDR phenotypes in gastric and pancreatic cancer cells through activation of caspase-3 (Reis et al., 2016). Regarding Hu et al. (2018) results, *E. sororia* is primarily found in northwest China and Central Asia, however, given the worldwide distribution of the genus and lack of research of the African flora, similar species native to Africa could be of interest to find similar diterpenes. Generally, these compounds have shown better results than the positive control compounds in several tests, as well as low toxicity and potentially better therapeutic indexes (Hu et al., 2018; Zhu et al., 2016). With more research, these jatrophanes truly hold promise to perhaps become the first clinically available P-gp modulators. It should also be noted that results regarding the compound from *E. paniculata* were included given that the species is reported in North Africa, but the subspecies has so far only been found in Portugal (Kew Royal Botanic Gardens).

As mentioned, jatrophanes also exhibited moderate proapoptotic cytotoxicity against various cancer cells (Bahmani et al., 2017; Fattahian et al., 2020; Ling et al., 2019; Reis et al., 2016). Notably, different

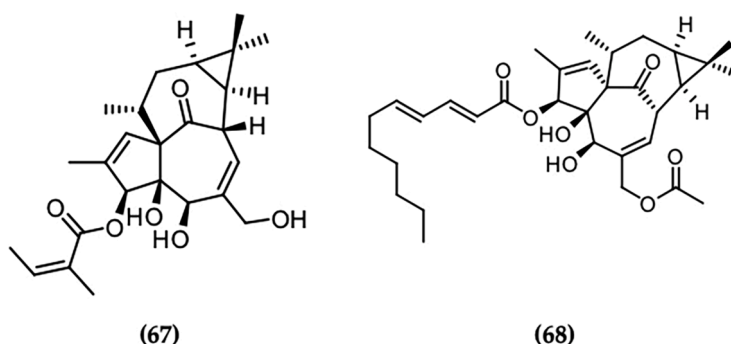


Fig. 16. Chemical structure of ingenane diterpenes ingenol mebutate (67) and 3EZ, 20Ac-ingenol (68).

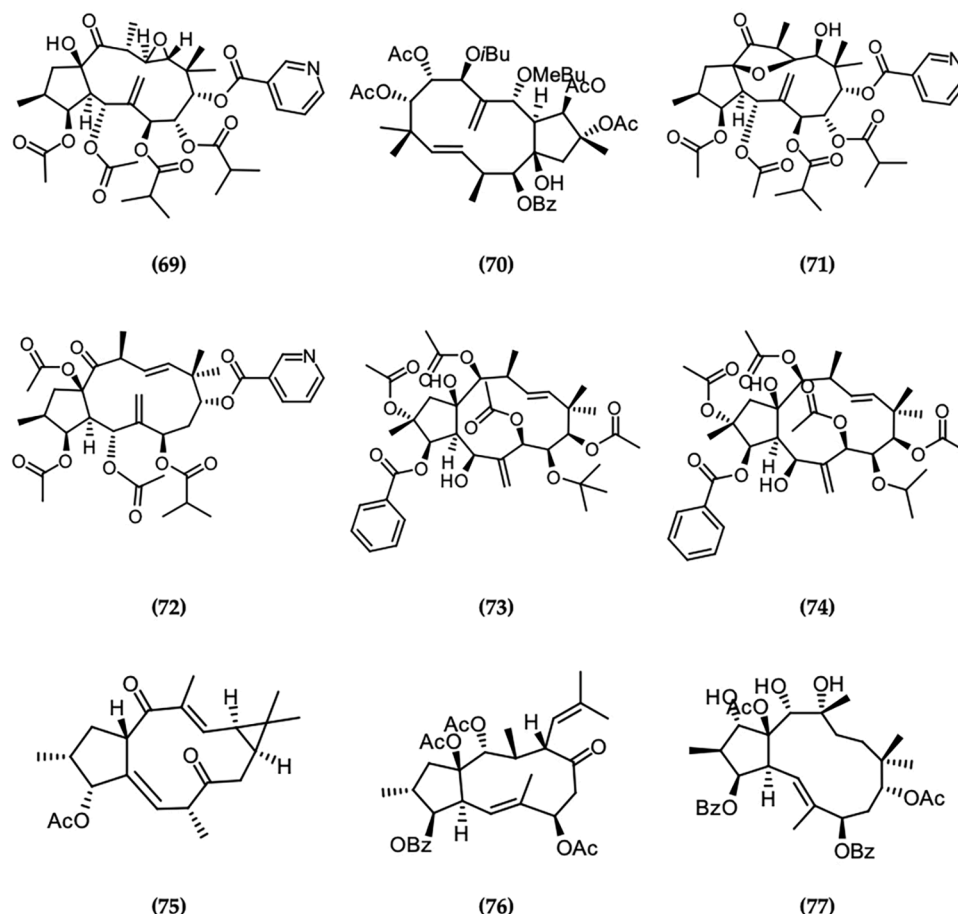


Fig. 17. Chemical structures of jatrophone diterpenes epoxywelwitschene (69), euphosorophane A (70), welwitschene (71), esulatin M (72), compound (73), compound (74), jatrogossone A (75), compound (76) and compound (77).

mechanisms of action were reported for the cytotoxicity of these diterpenes. Reis et al. (2016) reported the activation of caspase-3. On the other hand, in two studies by the same group (Bahmani et al., 2017), two jatrophanes (73) and (74) from the 2,3,5,7,8,9,14,15-octahydroxy-jatropha-6(17),11E-diene class from *Euphorbia osyridea* Bioss. induced both late and early apoptosis via accumulation of ROS and the mitochondrial pathway. Similarly, Ling et al. (2019) reported that jatrogossone A (75) from invasive species *Jatropha gossypifolia* L. (Euphorbiaceae) induced the reversible and selective upregulation of mitochondrial ROS, inducing mitophagy, as seen through live cell imaging. Interestingly, (75) induced cell death in a time-dependent manner, likely through cell cycle arrest at the G2/M stage *in vitro*, activation of caspase (3/7) and cleavage of PARP-1 (Ling et al., 2019).

Inflammation plays a significant role in cancer development and progression. Targeting it offers an appealing strategy for cancer prevention and therapy, as genetically stable cancer-associated inflammatory cells are less prone to drug resistance and contribute to malignant progression (Singh et al., 2019). In this context, Su et al. (2019) obtained a novel macrocyclic diterpene (76) that stands out as the third member discovered to date in a rare class of *Euphorbia* diterpenes, characterized by an unusual 5/10 fused ring system. This diterpene holds remarkable potential as an inhibitor of the initial phase of the inflammatory cascade initiated by LPS, as reported, through suppression of the secretions of crucial proinflammatory mediators IL-6 and TNF- α . This suppression is due to regulation of the NF κ B signalling pathway and evasion of the translocation of the p65 subunit (Su et al., 2019).

Furthermore, Zhu et al. (2016), described jatrophone (77) from *Pedilanthus tithymaloides* (L.) Poit. that, when co-administrated with DOX, demonstrated greater chemo-reversibility than DOX alone *in vivo*,

effectively restoring sensitivity of MDR tumours to chemotherapy at well-tolerated doses (Zhu et al., 2016).

Jatrophanes are promising compounds that could be developed as P-gp modulators. There are very interesting results from non-African compounds (69), (70), (71) and (72) as P-gp efflux modulators, which should encourage further research of the African compounds. Particularly, P-gp modulator (77) could be further studied using different cancer cell lines, co-administration with other cancer agents and, possibly, drug-like properties. For other jatrophanes, more detailed studies regarding the mechanisms of action as well as *in vivo* studies are a clear future direction (Fig. 17).

Lathyrane

Lathyrane diterpenes, predominantly found in the *Euphorbia* genus, have been reviewed in depth regarding their phytochemistry, synthesis of derivatives and pharmacological activities in a recent work (Vela et al., 2022). They are characterized by their chemical structure of a diterpene backbone with a lactone ring (which is a highly oxygenated tricyclic system of 5, 11 and 3 members). The structure of the lathyrane skeleton could be considered privileged because its arrangement makes interactions possible with multiple targets. These compounds are usually substituted with various acyl groups; some of the most frequently found ones, from natural sources, are acetyl, benzoyl and phenylacetyl groups. Methoxyl, tiglyl, or cinnamoyl groups are also quite widespread in lathyrane from natural sources. In fact, the acylation pattern was a critical factor in the reversal of MDR, where aromatic moieties were of fundamental importance (Vela et al., 2022).

Natural lathyrane diterpenes have been compiled in Table 1, showing activity in several cancer cell lines (lung, breast, ovary,

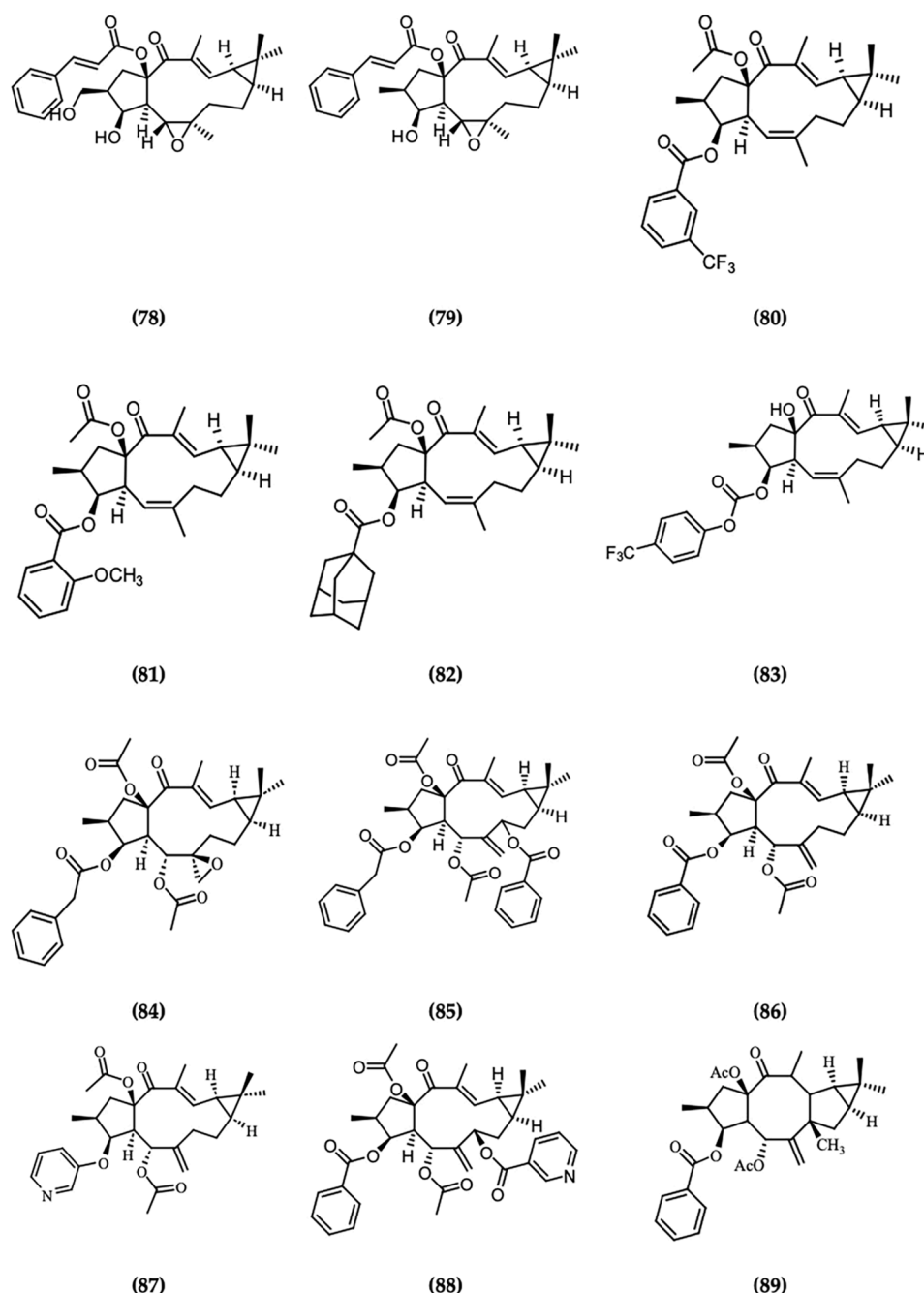


Fig. 18. Chemical structures of lathyrane diterpenes latilgascene B (78), jolkinol B (79), jolkinolate L (80), jolkinolate P (81), jolkinolate U (82) and jolkinolate B (83), euphorbia factor L1 (84), euphorbia factor L2 (85), euphorbia factor L3 (86), euphorbia factor L8 (87), euphorbia factor L9 (88), euphorbia Factor L15 (89) and compound (90).

lymphoma, etc.). Mechanistically, they induced intrinsic apoptosis and interacted with P-gp to overcome drug resistance (Nabatchian et al., 2017; Neto et al., 2019; Pusztai et al., 2007; Teng et al., 2018; Yang et al., 2020).

Moreover, the lathyrane diterpene latilgascene B (78) possessed synergistic interactions with doxorubicin, while jolkinol B (79) worked synergistically with paclitaxel, promoting tubulin from soluble to insoluble states and increased binding of paclitaxel to microtubules. Another relevant aspect of lathyrane diterpenes is that some of them showed collateral sensitivity against resistant cell lines (Vela et al., 2022).

The macrocyclic diterpenes gathered the attention of medicinal chemists due to their high structural diversity and their

pharmacologically relevant biological properties, which include anti-cancer properties (Reis et al., 2014). One of the main sources of this class of compounds include several species of *Euphorbia* genus, namely *Euphorbia piscatoria* Ait., a plant that can be found in Canary Islands geographically located north-west of Africa (Reis et al., 2012).

The primary cause of chemotherapy failure is MDR resulting from active drug efflux mediated by ATP-binding cassette (ABC) transporters. P-gp is a crucial ABC transporter implicated in MDR and serves as a significant target for overcoming drug resistance. With the goal of surmounting MDR in cancer and driven by previous findings demonstrating the potent P-gp modulatory activity of numerous macrocyclic diterpenes extracted from various species within the *Euphorbia* genus, Ferreira and colleagues conducted a series of investigations focusing on macrocyclic

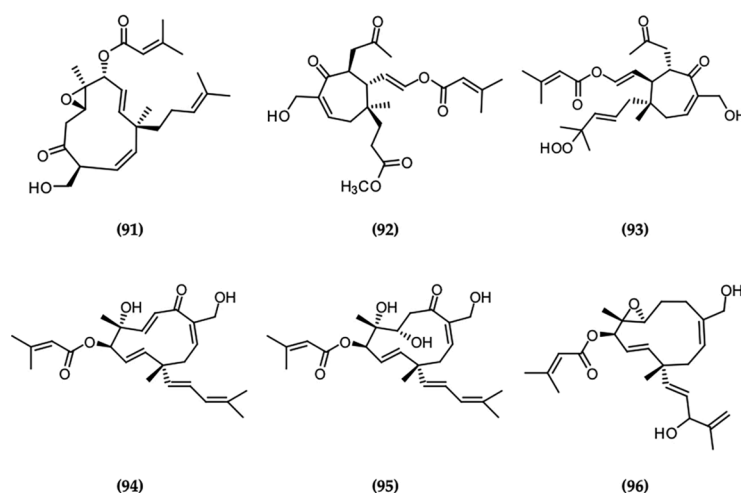


Fig. 19. Chemical structures of visbane diterpenes visbanol C (91), compound (92), vibsanin K (93), vibsanin B (94), visbanol I (95) and vibsanin S (96).

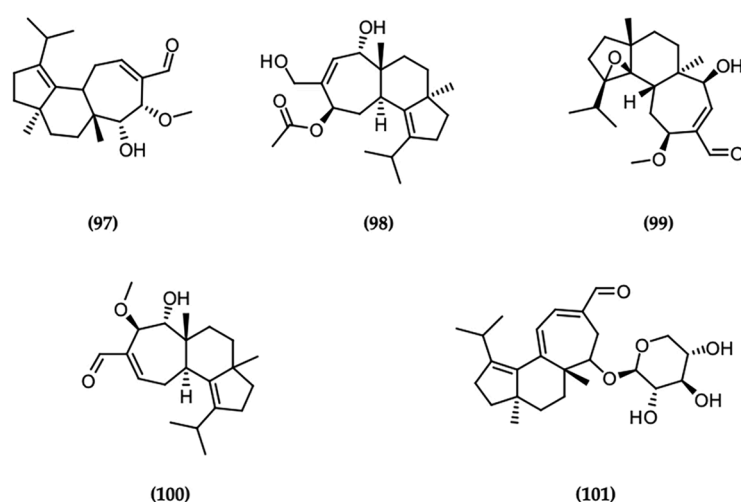


Fig. 20. Chemical structures of cyathane diterpenes neosarcodonin O (97), 11-O-acetylcathatriol (98), cyathin H (99), cyathin Q (100) and erinacine A (101).

diterpenes derived from *E. piscatoria*. They initially employed jolkinol D, a macrocyclic diterpene, as a starting point to prepare a series of derivatives that were tested for their ability to modulate P-gp efflux activity through a combination of transport and chemosensitivity assays, using the L5178 mouse T lymphoma cell line transfected with the human *MDR1* gene (Reis et al., 2013). Jolkinol D was inactive, but the introduction of an aromatic moiety improved the inhibition of this efflux pump at noncytotoxic doses (Reis et al., 2013). Moreover, these derivatives were evaluated for their collateral sensitivity effects, of which jolkinolate L (80) displayed an interesting MDR-selective antiproliferative activity (Reis et al., 2014). Thus, in the continuation of this anti-MDR development project, jolkinol D and jolkinodiols scaffolds were optimized and yielded a set of new derivatives among which jolkinolate P (81) exhibited strong modulation of P-gp activity, suggesting the importance of electron-donating groups in the aromatic moiety for optimal function. Moreover, derivatives (82) and (83) that were accessed for their collateral sensitivity effect, displayed promising MDR-selective antiproliferative activity and induced apoptosis through caspase 3 activation in resistant cancer cell lines, as evaluated using drug-sensitive and drug-resistant cell models of gastric and pancreatic tumors (Reis et al., 2017).

The research on macrocyclic diterpenes from *E. piscatoria* highlighted their potential as MDR reversers in cancer therapy. By targeting P-gp, these compounds showed promising results in overcoming drug

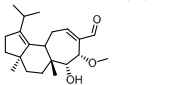
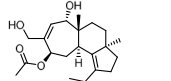
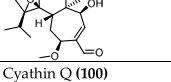
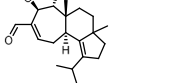
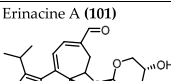
resistance mechanisms. However, further studies are warranted to explore their efficacy *in vivo* and elucidate their precise mechanisms of action.

Macrocyclic diterpenes (80), (81), (82) and (83) are reported to decrease P-gp efflux activity and could hold potential as MDR reversal agents. Further studies should focus on *in vivo* results. In the lathyrane class, there are several encouraging results with compounds presenting noteworthy IC_{50} values against several cancer cell lines amongst lathyrans afforded from *Euphorbia piscatoria*. As such, *in vivo* studies are necessary. This is also true for other lathyrans reported, as no *in vivo* results have been reported. Moreover, compound (79) is also of great interest as an MDR reversal agent, and *in vivo* studies are as of now a necessity. Reports of synergy of (78) with DOX and (79) with paclitaxel promote the evaluation of other lathyrans for similar results (Fig. 18).

Visbane

Known for its fast-growing, low maintenance and hardy characteristics, with fragrant white flowers in spring and early summer, *Viburnum odoratissimum*, although not indigenous, is grown ornamentally in Africa (Zhang et al., 2021). Visbane-type diterpenes extracted from this species exerted potent anticancer activities through a variety of mechanisms, against many cell lines, including HL-60, A549, SMMC-7721, MCF-7 and SW480, with one compound, visbanol C (91), showing significant cytotoxicity with IC_{50} values of 3.35, 4.41, 5.18, 11.30 and 3.70 μ M,

Table 2
Anti-cancer activity of diterpenes from **fungi** (and their semi-synthetic analogues), their mechanism(s) of action and, where relevant, associated preclinical and clinical data.

Class		Name and structure	Origin (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
TRICYCLIC	Cyathane	Neosarcodonin O (97) 	Cyathus africanus (culture)	In vitro (MTT assay)	Hela	IC ₅₀ = 5.86 μM (72 h)	Nitric oxide production (inflammation)	Significant ↓ of nitric oxide production in macrophages, with IC ₅₀ = 12.06 μM	(Han et al., 2013)
		K562			IC ₅₀ = 3.68 μM (72 h)				
		11-O-acetylcyathatriol (98) 			Hela	IC ₅₀ = 5.68 μM (72 h)		Significant ↓ of nitric oxide production in macrophages, with IC ₅₀ = 10.73 μM.	
		K562			IC ₅₀ = 8.64 μM (72 h)				
		Cyathin H (99) 			Hela	IC ₅₀ = 23.72 μM (72 h)			
K562	IC ₅₀ = 39.46 μM (72 h)								
		Cyathin Q (100) 		In vitro (Annexin-V/PI staining and immunofluorescence)	HCT116	10 mM, 24h: ↑ apoptotic cells to 82.07 % in HCT116 colon cancer cells.	Apoptosis. Flow cytometry analysis showed dose-dependent ↑ of ROS and Mito-SOX, activating JNK pathway.		(He et al., 2016)
				In vivo (xenograft tumor growth on mice)		↓ in tumour volume by 26.0 % (5 mg/kg) and 62.2 % (10 mg/kg)		5 or 10 mg/kg cyathin Q daily i.p. over 14 days:	
		Erinacine A (101) 	Hericum erinaceus (cultured mycelia)	In vitro (MTT Cell Viability Assay; Cell-cycle distribution analysed using flow cytometry; kinase signalling pathway activation by Western blot analysis)	DLD-1	10 μM erinacine A for 24 h, resulted in 64% of DLD-1 cells survived	24-h treatment with 10 uM erinacine A → G1 arrest in a time dependent manner: % of G1 phase cells ↑ to 54 ± 4 (6 h), 68 ± 2 (12 h), and 75 ± 2% (24 h), respectively. ROS; 20-fold ↑ of ROS production at 24 h with 10uM erinacine A → of mTOR/p70S6K/ NF-κB and p21 pathways		(Lu et al., 2016)
				In vivo (DLD1 cells xenografted into nude mice, % tumour volume reduction)		Intraperitoneal injections of erinacine A (1, 2 and 5 mg/kg/day) for 18 days after cell implantation resulted in ↓ to 42, 51, and 66% (P < 0.05), respectively, of those in the control group			

respectively (Li et al., 2022).

In a similar study, an active compound (92), which belongs to the visbane diterpene class, exhibited remarkable cytotoxic effects against A549 cells. The potency of (92) was quantified using MTT assay by its IC₅₀ value, which was determined to be 1.11 μM. To explore the

potential apoptotic effects of the compound, morphological changes in A549 cells were carefully observed under a phase contrast microscopy. Following treatment with (91), distinct morphological alterations associated with apoptosis, such as cell shrinkage and membrane blebbing, were observed. These observations were further confirmed

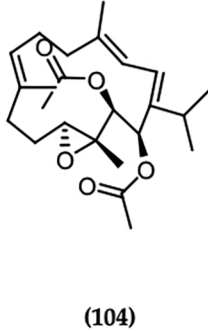
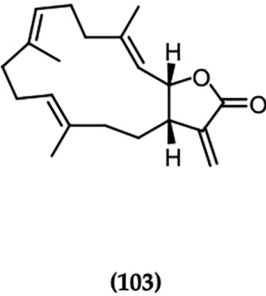
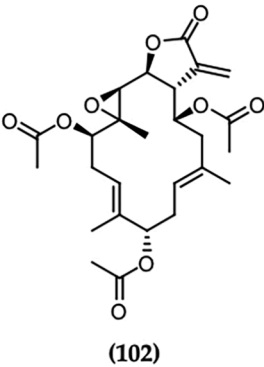
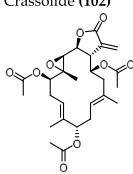
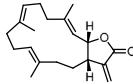
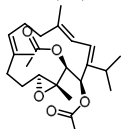


Fig. 21. Chemical structures of cembrane diterpenes from marine life crassolide (102), LS-1 (103) and flaccidoxide-13-acetate (104).

Table 3
Anti-cancer activity of diterpenes from **marine life** (and their semi-synthetic analogues), their mechanism(s) of action and, where relevant, associated preclinical and clinical data.

Class	Name and structure	Origin (part)	Experimental model(s)	Cell line(s)	Result(s)	Mechanistic pathway(s) targeted	Further information	References
MACROCYCLIC	Crassolide (102) 	<i>Lobophytum crassum</i>	<i>In vitro</i> (MTT, colony formation)	H460 H1299	IC ₅₀ = 10.2 ± 3.5 μM (24 h) IC ₅₀ = 19.3 ± 4.1 μM (24 h)	↑ G2/M phase arrest and apoptosis ↓ of mitogen-activated protein kinase 14 activation		(Lai et al., 2022)
	LS-1 (103) 		<i>In vitro</i> (MTT assay, hoechst 33342 staining, flow cytometric analysis of apoptosis and Western blot analysis)	SNU-C5	IC ₅₀ = 6.5 μM (72 h)	→ apoptosis via the downregulation of Wnt/β-catenin pathway and the activation of TGF-β pathway. ↓ β-catenin level through GSK-3β activation	Cell death by apoptosis: ↑ of sub-G1 hypodiploid cells and apoptotic bodies. ↑ the level of Bax & ↓ the level of Bcl-2 in a time dependent manner → cleavage of caspase-3 and cleavage of PARP	(Kim et al., 2016)
	Fractions G, I, and J of ethyl acetate extract.	<i>Virgularia gustaviana</i>	<i>In vitro</i> (Immunocytochemistry and Western Blot)	HeLa MDA-MB-231	↑ expressions of caspase-3 and caspase-8 in HeLa cells	Apoptosis	Study did not fully identify the specific compounds responsible for these anticancer effects.	(Sharifi et al., 2018)
	Flaccidoxide-13-acetate (104) 	<i>Simularia gibberosa</i>	<i>In vitro</i> (MTT, Boyden and Transwell chamber assays, gelatine zymography, Western Blotting)	HA22T HepG2	Dose-dependent ↓ in cell viability and ↓ of migration in concentration-dependent manner.	8 μM (24 h) migratory capacities were ↓ to 85% and 80% for HA22T and HepG2 cells, respectively. ↑ protein levels of N- and E-cadherin, while β-catenin, vimentin, and Snail levels ↓	→ the activities of MMP-2, MMP-9, and uPA in a dose-dependent manner. ↓ levels of MMP-2, MMP-9, MMP-13, and uPA proteins, while TIMP-1 and TIMP-2 expressions ↑ in HA22T and HepG2 cells (24 h) decreases in the protein levels of FAK, p-PI3K, mTOR, and p-mTOR	(Wu et al., 2020)

through Hoechst 33342 staining assay, which revealed nuclear fragmentation and chromatin condensation compared to the control group. Additionally, an annexin V-FITC/PI assay provided further confirmation of apoptosis induction. Apoptosis, a process often mediated by ROS-mediated oxidative stress, was investigated to determine if (**92**) induces this pathway. An increase in DCF fluorescence was observed upon H2DCF-DA staining, indicating a significant upregulation of intracellular ROS levels with increasing concentrations of (**92**). Furthermore, MitoSOX staining was employed to detect mitochondrial ROS levels and the fluorescence intensity gradually increased with higher concentrations of (**92**) compared to the control condition. Excessive ROS can disrupt the MMP, which is considered a key indicator of mitochondrial dysfunction and ultimately leads to apoptosis. JC-1 staining indicated a loss of MMP in A549 cells treated with (**92**), supporting its apoptotic effects on A549 cells (Li et al., 2021).

Additionally, other visbane-type diterpenes from *V. odoratissimum* were assessed for their anticancer activity and mechanism of action. HSP90 proteins play crucial roles in vital cellular processes and regulatory pathways, including apoptosis, cell cycle control, cell viability, protein folding and degradation, as well as signalling events. One such visbane-type diterpene exhibited significant cytotoxic effects against multiple cell lines, including HL-60, A-549, SMMC-7721, MCF-7 and SW480. The IC₅₀ values for these cell lines were measured as 0.15 ± 0.01, 0.69 ± 0.01, 0.41 ± 0.02, 0.75 ± 0.03 and 0.48 ± 0.03 μM, respectively. The HSP90 dependent luciferase refolding assay identified vibsantin K (**93**) as an inhibitory compound against HSP90, with an IC₅₀ value of 19.16 μM. Interestingly, the acetylated derivatives of these visbane-type compounds demonstrated even higher cytotoxicity compared to the unmodified forms (Zhu et al., 2018).

In addition to the promising results obtained from *in vitro* studies, the effectiveness of an ethyl acetate extract of *V. odoratissimum* (EAVO) containing various visbane diterpenes was assessed *in vivo* against HCC, the sixth most common cancer and the third leading cause of cancer-related deaths worldwide in 2020. Due to limited understanding of the molecular mechanisms underlying HCC, only a few first-line therapeutic drugs, such as sorafenib and lenvatinib, have been approved. Initially, KEGG analysis revealed that EAVO operates through multiple cancer-related pathways, including TNF, PI3K/AKT, Toll-like receptor, Hippo, Relaxin, PPAR, AMPK, mTOR, FoxO and p53. Specifically, EAVO exhibited anti-HCC activity by inhibiting the PI3K/AKT pathway. Furthermore, the researchers established a xenograft model in mice implanted with Hep3B cells. The administration of EAVO at doses of 100 mg/kg or 200 mg/kg significantly inhibited tumor growth, as evidenced by the notable reduction in tumor volumes and weights compared to the control group. Throughout the treatment period, there were no significant differences in body weights among the experimental groups. Additionally, no observable changes in major organs were observed between the control and EAVO-treated groups. EAVO treatment led to a significant decrease in the proliferation-related biomarkers Ki67 and p-AKT, while the ratio of Bax-positive cells was increased in the tumour sections. These findings indicated that EAVO effectively suppressed tumour growth in a nude mouse model without causing notable toxicity to organ function. Interestingly, the authors not only assessed the extract but also the major compounds in the EAVO and found that, similarly to EAVO, vibsantin B (**94**), vibsanol I (**95**), and vibsantin S (**96**) induced apoptosis by inhibiting the PI3K/AKT pathway and induce mitochondrial damage and oxidative stress in HepG2 cells (Xue et al., 2023).

Future studies should focus on elucidating the precise mechanisms

underlying the cytotoxic effects of compounds (91), (92), (93), (94), (95) and (96), and on testing the efficacy of the compounds and extract EAVO against other cancer cell lines. Further studies regarding the *in vivo* efficacy of individual compounds would also prove interesting (Fig. 19).

As demonstrated thus far in this review, diterpenes extracted from plants have very promising and real implications in the domain of cancer research. From the repurposing of *Coffea* spp. to harness the anticancer activity of kahweol (55) and cafestol (56); to the MDR reversal potential of jatrophanes, lathyranes and macrocyclic diterpenoids, such as epox-ywelwitschene (69), latilagascene B (78) and jolkinolate L (80), respectively; to the synergistic effects of phenolic diterpenes, such as carnosic acid (22) and carnosol (23); to potentially undiscovered African spp. containing cytotoxic *ent*-labdanes from *Aleuritopteris* spp. and *ent*-kauranes from *Isodon* spp., these diterpenoids could prove vital in the development of novel cancer therapeutics (Table 1).

Anti-cancer activity of diterpenes from fungi

Tricyclic

Cyathane diterpenes

Despite the large sways of attention and exploration that plants have received for their potential sources of lead molecules, research on fungi is on the up. It is estimated that fungi out-numbers plants by around 6 to 1, prompting the necessary consideration of this kingdom as a potential source of drug candidates (Blackwell, 2011). Cyathane diterpenes are natural compounds found in several species of fungi that have shown tumour growth inhibition and induced cancer cell death in animal models of breast, lung, and colon cancer (Chen et al., 2022). Cyathane diterpenes also have low toxicity in healthy cells, making them a potential candidate for chemotherapy. In this regard, several cyathane diterpenes, neosarcodonin O (97), and 11-O-acetylcycathatriol (98), isolated from *Cyathus africanus*, demonstrated good cytotoxic activity in two cancer cell lines, Hela and K562, with IC₅₀ values less than 10 µM, with an additional diterpene, cyathin H (99), showing moderate cytotoxicity with an IC₅₀ value of 23.72 and 39.46 µM, respectively. Additionally, the authors examined the anti-inflammatory ability of the cyathanes, demonstrating significant anti-inflammatory action. Since excessive production of NO is implicated in various diseases, such as cancer, by inhibiting its overproduction in cells, it may be possible to prevent the onset of inflammatory diseases and cancer (Han et al., 2013). The same research group identified another cyathane diterpene, cyathin Q (100), from the culture of the fungus *C. africanus*. Annexin-V/PI staining and immunofluorescence revealed that (100) (10 mM, 24 h) increased apoptotic cells to 82.07 % in HCT116 colon cancer cells. Flow cytometry analysis showed dose-dependent elevation of ROS and Mito-SOX by (100) in HCT116 cells. This led to (100)-induced apoptosis, altering cellular redox state and activating JNK pathway. *In vivo*, (100) (5 or 10 mg/kg) inhibited xenograft tumor growth by 26.0 and 62.2 %, respectively, over 14 days, without weight loss, discomfort or liver damage observed (He et al., 2016).

In addition, Lu et al. (2016) demonstrated an inhibitory effect on the growth of DLD-1 colorectal cancer cells using the cyathane diterpene erinacine A (101), found in the edible mushroom *Hericium erinaceus*. Cell cycle distribution analysis revealed that the administration of erinacine A resulted in G1 phase arrest in DLD-1 cells after a 24 h exposure to 10 µM erinacine A (101), attributed to the generation of ROS and the activation of mTOR/p70S6K/NF-κB/p21 pathways, known to regulate cell proliferation and cell cycle regulation. In addition, the authors found that the *in vivo* intraperitoneal injections of erinacine A (101) (1, 2 and 5 mg/kg/day) on nude mice significantly reduced DLD-1 tumour volume 18 days after cell implantation, to 42, 51 and 66 % (*p* < 0.05), respectively, of those in the control group, without signs of toxicity observed (Lu et al., 2016).

For a more in-depth analysis on the potential of cyathanes as drug

leads, a 2020 review can be consulted (Bailly and Gao, 2020).

Despite there being more identified fungi species than plant species, the literature about plants is far more extensive. Moreover, positive results from cyathanes from *Cyathus africanus*, make it evident that diterpenes from fungi have enormous potential as therapeutical agents and must be studied urgently. It would be interesting to see any of these compounds progress to clinical trials, however, for this, more robust mechanistic pathways must be established as well as more cell lines must be studied, and *in vivo* experiments carried out.

Overall, the fungi kingdom remains hugely unexplored, despite the enormous potential demonstrated as antitumor agents of different species, justified by the chemical richness of their biosynthesized compounds. Several cyathane diterpenes isolated from *Cyathus africanus*, such as neosarcodonin O (97) and 11-O-acetylcycathatriol (98), display potent cytotoxic activity against cancer cell lines, with additional anti-inflammatory effects. Research highlights the efficacy of cyathane diterpenes like cyathin Q (100) and erinacine A (101) in inhibiting tumour growth in colorectal cancer cells, both *in vitro* and *in vivo*, suggesting their potential as promising drug leads (Fig. 20, Table 2)

Anti-cancer activity of diterpenes from marine life

Macrocyclic

Cembrane

Covering two-thirds of the Earth's surface, the marine environment is characterised by an array of challenging conditions, including temperatures ranging from as low as -1.5 °C to as high as 350 °C, while pressure levels can range from 1 to over 1000 atmospheres. Despite its vastness, the marine environment remains largely unexplored, with less than 5% of the deep sea having been studied. Within this vast realm, approximately 240,000 known marine species exist. The challenging and competitive nature of this environment likely contributes to the production of unique metabolites by marine organisms. While terrestrial sources offer distinctive bioactive metabolites, marine organisms produce a substantial number of unprecedented bioactive substances, many of which hold great potential as lead drugs (Abdel-Lateff et al., 2019; Khalifa et al., 2019).

The search for anticancer drugs originating from marine sponges has yielded encouraging outcomes in recent years; for example, eribulin mesylate – the FDA approved simplified synthetic analogue of halichondrin B – is a compound isolated ~~for~~ from the marine sponge *Halichondria okadai*, found in Asia, for the treatment of malignant tumours, including metastatic breast cancer [Clinical Trials Identifier: NCT00337103]. This clinical trial was performed on patients with locally advanced or metastatic breast cancer who were previously treated with anthracyclines and taxanes. The overall survival after treatment with eribulin mesylate (doses of 1.4 mg/m²) was 87.4% (484/554). However, some adverse effects, such as neutropenia, leukopenia, pain, nausea, fatigue and appetite decrease were recorded [Clinical Trials Identifier NCT00337103].

Macrocyclic diterpenes, a diverse class of natural compounds, which are also found in numerous marine organisms, such as sponges and corals, have been identified for their potential anti-cancer properties, with several currently approved as chemotherapeutic drugs. For example, trabectedin, a tetrahydroisoquinoline alkaloid, binds to the minor groove of DNA and interferes with DNA repair mechanisms, ultimately leading to cell death, is used in the treatment of advanced soft-tissue sarcoma and ovarian cancer (European Medicines Agency, 2021). Other macrocyclic diterpenes, such as the toxic polyketide pederin family, produced by endosymbiotic bacteria of female beetles (*Paederus* and *Paederidus* genera), inhibit protein and DNA synthesis in cancer cells, leading to cell death (Piel et al., 2005). While these macrocyclic diterpenes have shown promise as potential chemotherapy agents, their clinical development has been hampered by challenges such as low yields from natural sources and complex synthesis.

Cembrane diterpenes, derived from marine organisms such as coral reefs and soft corals, show potential as anticancer agents. For example, crassolide (**102**), a cembranoid diterpene extracted from the soft coral south-east African coastline *Lobophytum crassum* exerted cytotoxic activity on H460 cancer cells by inducing G2/M phase arrest and apoptosis (Lai et al., 2022). In addition, compound (**102**) functions as an inhibitor of mitogen-activated protein kinase 14 activation, which emphasizes the immunotherapeutic properties of (**102**) in promoting anticancer immune responses (Lefranc et al., 2019). In fact, many of the current marine drugs approved for clinical trials are targeted for cancer therapy, yet none of them are from the diterpene family (Cappello and Nieri, 2021). Another marine cembrenolide diterpene LS-1 (**103**), extracted from *L. crissum*, was investigated for its mechanism of action, after being reported as having good cytotoxic activities. The MTT assay using human SNU-C5 colorectal cancer cells demonstrated an IC₅₀ value of (**103**) at 6.5 μ M. It induced apoptosis via the downregulation of Wnt/ β -catenin pathway and the activation of TGF- β pathway. The TGF- β signalling pathway was involved in various cellular processes, such as apoptosis, cell migration and cell differentiation. The cell death by apoptosis had typical characteristics, including increase of sub-G1 hypodiploid cells and apoptotic bodies. Treatment with (**103**) increased the level of Bax, a pro-apoptotic protein, while (**103**) decreased the level of Bcl-2, an anti-apoptotic protein, in a time dependent manner. In addition, treatment of (**103**) induced the cleavage of caspase-3, an executioner caspase, and cleavage of PARP in time-dependent manners. These results indicated that (**103**) inhibited the proliferation of SNU-C5 cells by the induction of apoptosis. Treatment with (**103**) decreased levels of phospho-GSK-3 β , the inactivated form of GSK-3 β and β -catenin. These data suggest that (**103**) might decrease β -catenin level through GSK-3 β activation and that the (**103**) effect on the apoptosis induction could be associated with the downregulation of the Wnt/ β -catenin signalling pathway. Compound (**103**) could activate TGF- β signalling with decrease of CEA, which is followed by the decrease of c-Myc in SNU-C5 cells (Kim et al., 2016).

Other marine organisms that have potential for cancer therapy include the sea pen *Virgularia gustaviana*, found along the South Africa coastline. The anticancer potential of this organism was explored using HeLa and MDA-MB-231 cancer cells by Sharifi et al. (2018), in which the ethyl acetate extract of *V. gustaviana* was investigated. Chromatographic fractions G, I and J contained compounds closely related to sarcophine, a well-known anticancer cembrane diterpenoid. Treatment with fractions G, I and J increased the expression of caspase-3 and caspase-8 in HeLa cells, resulting in apoptosis. Fraction G induced caspase-3 expression in approximately 90 % of HeLa cells, while fractions J and I induced it in about 87 and 90 % of the cells, respectively. Similarly, caspase-8 expression was induced in around 95, 95 and 88 % of HeLa cells treated with fractions G, I and J, respectively. In MDA-MB-231 cells, treatment with fraction G resulted in 78 % of cells expressing caspase-8, while fractions J and I induced caspase-8 expression in approximately 80 and 90 % of the cells, respectively. Additionally, caspase-3 was expressed in 88, 96 and 60 % of MDA-MB-231 cells treated with fractions G, I and J, respectively. Overall, the fractions from the ethyl acetate extract of *V. gustaviana* demonstrated their ability to induce apoptosis in cancer cells. Despite the promising results, the study did not fully identify the specific compounds responsible for these anticancer effects. Further research is needed to pinpoint the exact compounds responsible for the observed anti-cancer activity (Sharifi et al., 2018).

Liver cancer cases are predominantly found in sub-Saharan African countries, accounting for nearly 82 % of the total global cases. In the Asia-Pacific region, hepatitis B and C viruses are the primary causal factors, with chronic hepatitis B infections being the leading cause of liver cancer. Flaccidoxide-13-acetate (**104**), a cembrane-type diterpene obtained from *Sinularia gibberosa* along the coast of Tanzania, was subjected to an (MTT) assay to assess its cytotoxic effects on HA22T and HepG2 human HCC cell lines. The results revealed a dose-dependent reduction in cell viability for both HA22T and HepG2 cells upon

treatment with (**104**). Moreover, Boyden and Transwell chamber assays were conducted on the same cell lines to evaluate their migratory and invasive properties, indicating that flaccidoxide-13-acetate inhibited the migration of HA22T and HepG2 cells in a concentration-dependent manner. Notably, after treating the cells with an 8 μ M concentration of (**104**) for 24 h, their migratory capacities were reduced to 85 and 80 % for HA22T and HepG2 cells, respectively. To investigate the impact of (**104**) on the activities of MMP-2, MMP-9 and uPA, gelatin zymography was employed to assess their levels in HA22T and HepG2 cells. Compound (**104**) effectively inhibited the activities of MMP-2, MMP-9 and uPA in a dose-dependent manner. Furthermore, Western blotting was employed to evaluate the influence of (**104**) on the expression of MMP-2, MMP-9, MMP-13, uPA, TIMP-1 and TIMP-2 proteins. The findings indicated decreased levels of MMP-2, MMP-9, MMP-13 and uPA proteins, while TIMP-1 and TIMP-2 expressions increased in HA22T and HepG2 cells following treatment with (**104**) for 24 h. Focal adhesion kinase (FAK) is a cytoplasmic protein kinase involved in regulating cell motility, survival, and proliferation. Overactivation of FAK has been linked to tumour progression and metastasis. To explore how (**104**) affects FAK activity and downstream signalling in HA22T and HepG2 cells, the authors employed Western blotting to assess the expressions of FAK, PI3K, AKT, mTOR, p-PI3K, mTOR and p-mTOR proteins. The protein levels of FAK, p-PI3K, mTOR and p-mTOR were decreased, indicating the inhibitory effects of (**104**) on these molecules. Epithelial-mesenchymal transition (EMT) is a critical process in tumour metastasis, where epithelial cells lose their adherence and transform into mesenchymal cells. In EMT, Snail, a key transcription factor, suppresses E-cadherin transcription, while vimentin regulates β -catenin translocation. To investigate whether (**104**) inhibits EMT in HA22T and HepG2 cells, Western blotting was used to measure the levels of cytosolic β -catenin, N-cadherin, E-cadherin, vimentin, and nucleic Snail. The results demonstrated increased protein levels of N- and E-cadherin, while β -catenin, vimentin and Snail levels decreased in HA22T and HepG2 cells after (**104**) treatment (Wu et al., 2020).

Future scientific studies should focus on elucidating the precise mechanisms underlying the anticancer activity of cembrane diterpenoids, particularly in liver cancer therapy. *In vivo* studies are also necessary. It would be particularly interesting to have *in vivo* results with mice bearing liver tumours for compound (**104**), given the high prevalence of liver cancer in the region. Individual cytotoxic compounds from *V. gustaviana* must also be identified. Additionally, identifying and characterizing novel cembrane diterpenoids from marine organisms, such as soft corals and sea pens, could expand the repertoire of potential anticancer agents derived from marine sources.

Marine organisms produce unique metabolites, many of which hold potential as lead drugs, contributing to the search for anticancer agents. Indeed, macrocyclic diterpenes in marine organisms, with cembrane diterpenes, particularly from coral reefs and soft corals, demonstrate anticancer potential. Compounds like crassolide (**102**) and LS-1 (**103**) have shown their cytotoxic activity against cancer cells through various mechanisms. Flaccidoxide-13-acetate (**104**), also obtained from marine sources, exhibits cytotoxic effects through modulating MMP and FAK signalling pathways and influencing EMT, a critical process in tumour metastasis, demonstrating the importance of pursuing natural product research in marine environments (Fig. 21, Table 3).

Synergy vs. isolate

In most articles reviewed, the compounds were evaluated as individual isolates. However, it is widely acknowledged and documented that in certain instances total herb extracts exhibit superior efficacy compared to isolated compounds, despite the lack of a clear understanding for this phenomenon (Williamson, 2001). In fact, in this review, we highlighted such is the case for the ethyl acetate extract of *V. odoratissimum* in which the extract showed promising tumour reduction in a xenograft mouse model (Xue et al., 2023). Indeed, in cancer

therapy, many drugs are used in combination to enhance the synergistic effects (if a plant extract is more than the sum of its parts), indicating the inherent need for further research in drug-drug combinational vs. isolated drug therapy (Wagner and Ulrich-Merzenich, 2009). Our literature search found such an example from the active components of rosemary, carnosic acid (22) and carnosol (23), which demonstrate synergistic effects with other antineoplastic agents (Vergara et al., 2014). A potential approach with the capacity to enhance the existing therapeutic cancer model involves combining anticancer drugs with bioactive phytochemical components from medicinal plants or plant extracts. This combination of hybrid compounds can exhibit synergistic effects on multiple targets and signalling pathways, offering a promising avenue for expanding the effectiveness of cancer treatments (Domínguez-Martín et al., 2019). In addition to this, the current Western paradigm for approaching health and well-being is centred around the ‘magic/silver bullet’ ideal with an ambition to formulate mono-therapeutic drug treatment models. However, in traditional medicinal systems, herbal combinations are more commonplace. For example, a study demonstrated synergistic effects in the inhibition of human breast cancer cell line growth when pairs of flavonoids, specifically genistein, baicalein, hesperetin, naringenin, and quercetin were combined (Wagner and Ulrich-Merzenich, 2009). In many developing and developed nations, including African, the integration of traditional medicine systems in hospitals is not uncommon, yet the efficacy of implementation and adoption of traditional knowledge is limited (Ampomah et al., 2020).

Bioprospecting in the African continent

The process of exploring and studying biological resources in Africa, such as plants and fungi, to discover and develop new products, technologies or applications faces various challenges and problems. Fair and equitable sharing of benefits derived from the use of African biodiversity is a major concern related to intellectual property rights. In the past, affluent nations have historically exploited natural resources, found in biodiverse regions, particularly during periods of colonization, where empires appropriated resources from the territories they controlled. These resources, once patented and exported, have facilitated significant advancements in medicine, agriculture, and cosmetics. However, many of these breakthroughs rely heavily on traditional knowledge from indigenous communities, often without proper accreditation or compensation for their contributions. Failure to provide appropriate compensation or recognition to local communities and indigenous peoples for the exploitation of genetic resources and traditional knowledge can result in biopiracy and an imbalanced distribution of benefits. Furthermore, the insufficient research capacity, inadequate scientific infrastructure, and limited funding for bioprospection activities impede the comprehensive exploration and utilisation of Africa’s biodiversity. Insufficient investment in research and development restricts the ability to study, comprehend and fully leverage the potential of African biological resources. Compared to the other areas of the world, it was apparent when conducting this literature survey that far more research has been conducted in Asian countries compared to African nations. In fact, in 2019, Asian medicinal plants accounted for approximately 45% of the global earnings from traditional medicines, highlighting Asia’s striking market lead in drug research using medicinal plants (Astutik et al., 2019). Additionally, to demonstrate the extent to which African countries are trailing behind in natural product research, the Nature Index 2023 Annual Table, which unveils the leading countries in natural and health sciences research, ranked the USA as dominating the field with the highest output in biological sciences, with China, UK, Germany and Japan following, respectively. The first mention of an African nation, South Africa, came in ranking at position 30, with Kenya following at position 41 (Nature, 2023). In order to give context for the disparity between clinical development of cancer drugs in Africa vs. the rest of the world, a simple search using the key term ‘cancer’ on ClinicalTrials.gov, for active (non-recruiting), interventional

clinical trials, documented the two highest ranking countries in the Nature Index 2023 Annual Table recorded an impressive 4249 trials in the USA and 796 in China. For African nations with the highest GDP, only 78, 24 and 10 clinical trials are registered and active for South Africa, Egypt and Kenya, respectively (National Library of Medicine).

Given that the African continent is home to 5 biodiversity hotspots, the immediate threat of climate change on the biodiversity of these regions is ever decreasing the likelihood of exploring all the current potential flora and marine life that may provide medicinally active compounds. It is essential to establish effective mechanisms for accessing genetic resources and traditional knowledge, ensuring fair and equitable sharing of benefits to the wisdom keepers of traditional knowledge. Clear policies, legal frameworks and regulations governing access to genetic resources and associated traditional knowledge are necessary to prevent exploitation and promote ethical bioprospecting practices. Bioprospecting should prioritise biodiversity conservation and sustainable utilisation of natural resources. Unregulated or unsustainable collection practices can harm ecosystems, leading to habitat destruction, overharvesting, and biodiversity loss. Implications of increased international interest in natural product drug development and an uneven balance of supply and demand can lead to severe overharvesting and, in some cases, endangerment, as was the case for both *Rhodiola rosea* and *Rhodiola crenulate*. It is crucial to ensure the long-term viability of ecosystems and the potential for future bioprospecting endeavours. Building scientific capacity, promoting knowledge transfer, and providing training opportunities for African researchers and local communities are vital to empowering local communities and indigenous peoples with skills, resources and expertise that will allow them to actively participate in and benefit from bioprospecting activities. With an increased interest in research of natural products from African nations, and the implementation of the Nagoya Protocol, one would expect a positive boost on the economy of these countries. Additionally, benefit-sharing agreements for fair and mutually beneficial arrangements between researchers, institutions and local communities are critical in ensuring just compensation, intellectual property rights protections and a share of economic benefits for local communities are vital to promote equity and prevent exploitation. However, the Nagoya Protocol, which mandates countries to share benefits from genetic resources equitably, is limited in efficacy by the lack of regulation in some countries regarding access to their genetic resources. This discrepancy puts nations with stricter regulations and benefit-sharing agreements at a disadvantage. In addition, the traceability and adherence to providing equitable sharing of profits is not always well established.

Conclusions

Diterpenes from African flora, fungi and soft corals have been shown to demonstrate their potency in multiple cancer cell lines, *in vitro* and *in vivo*, as well as the many mechanistic pathways. Certain diterpenes have showcased their potential to be investigated further in clinical settings as drug candidates for cancer therapy. Andrographolide (10), a lactone diterpene from *Andrographis paniculata*, and forskolin (6), a labdane diterpene isolated from *Coleus forskohlii* and known by the synonym *Plectranthus barbatus*, (only one clinical trial in cystic fibrosis) are among the prospective candidates. In addition, given the incredible number of *ent*-kauranes extracted from *Isodon*, and especially the encouraging results, such as for flexicaulin A (48) and its derivative (49), it is of interest to study the diterpenes of the two species of the *Isodon* genus found in Africa. Moreover, jatrophanes, such as euphosorophane A (70) from the fructus of *Euphorbia sororia*, with their diverse structures and unique capacity to act as possibly the firsts safe MDR-reversal agents, are of enormous interest. Also important in MDR cancers as Pgp modulators, derivatives of jolkinol D, a macrocyclic diterpene from *Euphorbia piscatorial*, show potential as chemotherapeutic drug candidates. Additionally, both kahweol (55) and cafestol (56) have presented themselves

as tremendously interesting agents in the treatment of cancer, with a variety of interfered pathways, rich biological activities relevant to cancer prevention and treatment, high selectivity and lack of toxicity. These *Coffea* diterpenes are of great interest, given the possibility of repurposing the already abundant coffee cultivation across the globe. From the fungi kingdom, the cyathane diterpene erinacine A (**101**), extracted from *Hericium erinaceus*, showed very promising *in vivo* results in mice models, compelling future studies to be directed on this diterpene.

Despite the promising data collected, one of the main concerns during the development of the new chemotherapeutic drugs is the safety profile, making it essential to assess if any of the mechanisms of action that drives the action of these anti-tumour agents, could potentially compromise their selectivity towards cancer cells vs non-malignant cells. Investigations into the bioavailability, pharmacokinetics, and safety profiles of these compounds are essential for their development as novel therapeutic agents. Additionally, comparative studies across different cancer types and exploration of potential synergistic effects with existing treatments could provide valuable insights into their clinical utility.

Finally, addressing the challenges associated with bioprospecting requires collaboration among governments, researchers, local communities, and international organisations. Comprehensive policies with strengthened research infrastructure and sustainable practices can foster responsible and equitable bioprospecting in Africa, preserving biodiversity and respecting the rights of local communities and indigenous peoples in the search for novel cancer therapeutics.

CRedit authorship contribution statement

Gabrielle Bangay: Writing – original draft, Methodology, Data curation. **Florencia Z. Brauning:** Writing – original draft, Data curation. **Andreia Rosatella:** Writing – original draft, Data curation. **Ana María Díaz-Lanza:** Visualization. **Eva María Domínguez-Martín:** Writing – original draft, Data curation. **Bruno Goncalves:** Writing – original draft, Data curation. **Ahmed A. Hussein:** Investigation. **Thomas Efferth:** Validation, Supervision, Conceptualization. **Patricia Rijo:** Writing – review & editing, Visualization, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Patricia Rijo reports financial support was provided by Universidade Lusófona. Patricia Rijo reports a relationship with Universidade Lusófona that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge and thank Fundação para a Ciência e a Tecnologia (FCT, Portugal), for funding this project through DOI 10.54499/UIDP/04567/2020, DOI 10.54499/UIDB/04567/2020. G.B. gratefully acknowledges Fundação para a Ciência e a Tecnologia (FCT, Portugal) for funding this project through UI/BD/151422/2021. E.M.D.-M. gratefully acknowledges being the recipient of a FPU 2019 fellowship from University of Alcalá. F.Z.B. acknowledges the support of Fundação Calouste Gulbenkian for this work N°. 275123.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.phymed.2024.155634](https://doi.org/10.1016/j.phymed.2024.155634).

References

- Abdel-Lateff, A., Alarif, W.M., Alburae, N.A., Algandaby, M.M., 2019. Alcyonium octocorals: potential source of diverse bioactive terpenoids. *Molecules*. <https://doi.org/10.3390/molecules24071370>.
- Acquaviva, R., Malfa, G.A., Loizzo, M.R., Xiao, J., Bianchi, S., Tundis, R., 2022. Advances on natural abietane, labdane and clerodane diterpenes as anti-cancer agents: sources and mechanisms of action. *Molecules*. <https://doi.org/10.3390/molecules27154791>.
- Adewole, K.E., 2020. Nigerian antimalarial plants and their anticancer potential: a review. *J. Integr. Med.* <https://doi.org/10.1016/j.joim.2020.01.001>.
- Ahmad, W., Jantan, I., Bukhari, S.N.A., 2016. *Tinospora crispa* (L.) Hook. f. & Thomson: a review of its ethnobotanical, phytochemical, and pharmacological aspects. *Front. Pharmacol.* <https://doi.org/10.3389/fphar.2016.00059>.
- Akaber, M., Mehri, S., Iranshahi, M., 2015. Multiple pro-apoptotic targets of abietane diterpenoids from *Salvia* species. *Fitoterapia*. <https://doi.org/10.1016/j.fitote.2014.11.008>.
- Akaber, M., Iranshahi, M., Mehri, S., 2016. Molecular signaling pathways behind the biological effects of *Salvia* species diterpenes in neuropharmacology and cardiology. *Phytother. Res.* <https://doi.org/10.1002/ptr.5599>.
- Al-Kenany, S.A., Al-Shawi, N.N., 2023. Protective effect of cafestol against doxorubicin-induced cardiotoxicity in rats by activating the Nrf2 pathway. *Front. Pharmacol.* <https://doi.org/10.3389/fphar.2023.1206782>.
- Alves, A.L.V., da Silva, L.S., Faleiros, C.A., Silva, V.A.O., Reis, R.M., 2022. The role of ingenane diterpenes in cancer therapy: from bioactive secondary compounds to small molecules. *Nat. Prod. Commun.* <https://doi.org/10.1177/1934578X221105691>.
- Ampomah, I.G., Malau-Aduli, B.S., Malau-Aduli, A.E.O., Emeto, T.I., 2020. Effectiveness of integrated health systems in Africa: a systematic review. *Medicina (Lithuania)*. <https://doi.org/10.3390/medicina56060271>.
- An, J., Li, L., Zhang, X., 2021. Curcucione C induces apoptosis in endometrial cancer cells via mitochondria-dependent apoptotic and ERK pathway. *Biotechnol. Lett.* <https://doi.org/10.1007/s10529-020-03027-4>.
- Ashrafzadeh, M., Zarrabi, A., Hashemi, Farid, Moghadam, E.R., Hashemi, Fardin, Entezari, M., Hushmandi, K., Mohammadinejad, R., Najafi, M., 2020. Curcumin in cancer therapy: a novel adjunct for combination chemotherapy with paclitaxel and alleviation of its adverse effects. *Life Sci.* <https://doi.org/10.1016/j.lfs.2020.117984>.
- Astutik, S., Pretzsch, J., Kimengsi, J.N., 2019. Asian medicinal plants' production and utilization potentials: a review. *Sustainability*. <https://doi.org/10.3390/su11195483>.
- Bahmani, B., Keyvanloo Shahrestanaki, M., Ghanadian, M., Hajiahmadi, S., Aghaei, M., 2017. Jatropho-6(17), 11 e -diene class derivatives induce apoptosis effects in OVCAR-3 and Caov-4 ovarian cancer cell lines via a mitochondrial pathway. *Biochem. Cell Biol.* <https://doi.org/10.1139/bcb-2017-0034>.
- Bailly, C., Gao, J.M., 2020. Erinacine A and related cyathane diterpenoids: molecular diversity and mechanisms underlying their neuroprotection and anticancer activities. *Pharmacol. Res.* <https://doi.org/10.1016/j.phrs.2020.104953>.
- Bakhtiar, H., Gheysarzadeh, A., Ghanadian, M., Aghaei, M., 2021. 15-Hydroxy-8(17), 13 (E)-labdadiene-19-carboxylic acid (HLCA) inhibits proliferation and induces cell cycle arrest and apoptosis in ovarian cancer cells. *Life Sci.* <https://doi.org/10.1016/j.lfs.2020.118981>.
- Balbinot, R.B., de Oliveira, J.A.M., Bernardi, D.I., Melo, U.Z., Zanqueta, É.B., Endo, E.H., Ribeiro, F.M., Volpato, H., Figueiredo, M.C., Back, D.F., Basso, E.A., Ruiz, A.L.T.G., de Carvalho, J.E., Foglio, M.A., Prado Filho, B.D., Nakamura, T.U., Nakamura, C.V., do Carmo, M.R.B., Sarragiotto, M.H., Baldoqui, D.C., 2019. Structural Characterization and Biological Evaluation of 18-Nor-ent-labdane Diterpenoids from *Grazziella gaudichaudiana*. *Chem. Biodivers.* <https://doi.org/10.1002/cbdv.201800644>.
- Barnett, C.M.E., Broit, N., Yap, P.Y., Cullen, J.K., Parsons, P.G., Panizza, B.J., Boyle, G. M., 2019. Optimising intratumoral treatment of head and neck squamous cell carcinoma models with the diterpene ester Tigilanol tiglate. *Invest. New Drugs* [37](https://doi.org/10.1007/s10637-018-0604-y). <https://doi.org/10.1007/s10637-018-0604-y>.
- Bassey, K., Mamabolo, P., Cosa, S., 2021. An andrographolide from *Helichrysum caespitum* (Dc.) sord. ex harv., (asteraceae) and its antimicrobial, anti-quorum sensing, and antibiofilm potentials. *Biology* [10](https://doi.org/10.3390/biology10121224). <https://doi.org/10.3390/biology10121224>.
- Beesetti, S.L., Jayadev, M., Subhashini, G.V., Mansour, L., Alwasel, S., Harrath, A.H., 2019. Andrographolide as a therapeutic agent against breast and ovarian cancers. *Open. Life Sci.* [14](https://doi.org/10.1515/biol-2019-0052). <https://doi.org/10.1515/biol-2019-0052>.
- Bezeng, B.S., Davies, T.J., Daru, B.H., Kabongo, R.M., Maurin, O., Yessoufou, K., Van Der Bank, H., Van Der Bank, M., 2017. Ten years of barcoding at the African Centre for DNA Barcoding. *Genome*. <https://doi.org/10.1139/gen-2016-0198>.
- Blackwell, M., 2011. The fungi: 1, 2, 3 ... 5.1 million species? *Am. J. Bot.* [98](https://doi.org/10.3732/ajb.1000298). <https://doi.org/10.3732/ajb.1000298>.
- Bodéde, O., More, G.K., Prinsloo, G., 2021. Antimicrobial, cytotoxic and oxidative stress inhibitory activities of terpenoids and flavonols from *Senegalia nigrescens* (Oliv.) P. J.H. Hurter. *Iran. J. Pharm. Res.* [20](https://doi.org/10.22037/ijpr.2021.115653.15463). <https://doi.org/10.22037/ijpr.2021.115653.15463>.
- Bouzas, A., Gómez de Cedrón, M., Colmenarejo, G., Laparra-Llopis, J.M., Moreno-Rubio, J., Montoya, J.J., Reglero, G., Casado, E., Tabares, B., Sereno, M., Ramírez de Molina, A., 2022. Phenolic diterpenes from Rosemary supercritical extract inhibit non-small cell lung cancer lipid metabolism and synergise with therapeutic drugs in the clinic. *Front. Oncol.* [12](https://doi.org/10.3389/fonc.2022.1046369), 1–22. <https://doi.org/10.3389/fonc.2022.1046369>.

- Buenz, E.J., Verpoorte, R., Bauer, B.A., 2018. The ethnopharmacologic contribution to bioprospecting natural products. *Annu. Rev. Pharmacol. Toxicol.* <https://doi.org/10.1146/annurev-pharmtox-010617-052703>.
- Rhett, A.B., 2020. Total Number of Plant Species by Country [WWW Document].
- Callaghan, R., Luk, F., Bewawy, M., 2014. Inhibition of the multidrug resistance P-glycoprotein: time for a change of strategy? *Drug Metabol. Dispos.* <https://doi.org/10.1124/dmd.113.056176>.
- Cappello, E., Nieri, P., 2021. From life in the sea to the clinic: the marine drugs approved and under clinical trial. *Life*. <https://doi.org/10.3390/life11121390>.
- Cardoso, P.C.dos S., Rocha, C.A.M.da, Leal, M.F., Bahia, M.de O., Alcântara, D.D.F.A., Santos, R.A.dos, Gonçalves, N.dos S., Ambrósio, S.R., Cavalcanti, B.C., Moreira-Nunes, C.A., Pessoa, C.do O., Burbano, R.M.R., 2017. Effect of diterpenoid kaurenoic acid on genotoxicity and cell cycle progression in gastric cancer cell lines. *Biomed. Pharmacother.* 89 <https://doi.org/10.1016/j.biopha.2017.02.085>.
- Catarino, L., Romeiras, M.M., 2020. Biodiversity of vegetation and flora in tropical Africa. *Diversity*. <https://doi.org/10.3390/d12100369>.
- Cavalcanti, B.C., Bezerra, D.P., Magalhães, H.I.F., Moraes, M.O., Lima, M.A.S., Silveira, E.R., Câmara, C.A.G., Rao, V.S., Pessoa, C., Costa-Lotufo, L.V., 2009. Kauren-19-ic acid induces DNA damage followed by apoptosis in human leukemia cells. *J. App. Toxicol.* 29 <https://doi.org/10.1002/jat.1439>.
- Chen, Yu Chi, Huang, B.M., Lee, W.C., Chen, Yung Chia, 2018. 16-Hydroxycleroda-3,13-dien-15,16-olide induces anoikis in human renal cell carcinoma cells: involvement of focal adhesion disassembly and signaling. *Oncotargets. Ther.* 11 <https://doi.org/10.2147/OTT.S173378>.
- Chen, H.Y., Lei, J.Y., Li, S.L., Guo, L.Q., Lin, J.F., Wu, G.H., Lu, J., Ye, Z.W., 2022. Progress in biological activities and biosynthesis of edible fungi terpenoids. *Crit. Rev. Food Sci. Nutr.* <https://doi.org/10.1080/10408398.2022.2045559>.
- Cheng, M.F., Lin, S.R., Tseng, F.J., Huang, Y.C., Tsai, M.J., Fu, Y.S., Weng, C.F., 2017. The autophagic inhibition oral squamous cell carcinoma cancer growth of 16-hydroxy-cleroda-3,14-diene-15,16-olide. *Oncotarget*. 8 <https://doi.org/10.18632/oncotarget.18987>.
- Chibas, L.C., Cintra, P.P., Moreira, M.R., Goulart, M.O., Ambrósio, S.R., Veneziani, R.C. S., Bastos, J.K., dos Santos, R.A., 2019. Polyalthic acid in polymeric nanoparticles causes selective growth inhibition and genotoxicity in MCF-7 cells. *Nat. Prod. Commun.* 14 <https://doi.org/10.1177/1934578x19842702>.
- Choi, D.W., Lim, M.S., Lee, J.W., Chun, W., Lee, S.H., Nam, Y.H., Park, J.M., Choi, D.H., Kang, C.D., Lee, S.J., Park, S.C., 2015. The cytotoxicity of kahweol in HT-29 human colorectal cancer cells is mediated by apoptosis and suppression of heat shock protein 70 expression. *Biomol. Ther. (Seoul)* 23. <https://doi.org/10.4062/biomolther.2014.133>.
- Choi, J.H., Hwang, Y.P., Jin, S.W., Lee, G.H., Kim, H.G., Han, E.H., Kim, S.K., Kang, K.W., Chung, Y.C., Jeong, H.G., 2019. Suppression of PMA-induced human fibrosarcoma HT-1080 invasion and metastasis by kahweol via inhibiting Akt/JNK1/2/p38 MAPK signal pathway and NF- κ B dependent transcriptional activities. *Food Chem. Toxicol.* 125, 1–9. <https://doi.org/10.1016/j.fct.2018.12.038>.
- Chung, J.Y., Lee, S.J., Lee, H.J., Bong, J.Bin, Lee, C.H., Shin, B.S., Kang, H.G., 2021. Aconitine neurotoxicity according to administration methods. *J. Clin. Med.* 10 <https://doi.org/10.3390/jcm10102149>.
- Corea, G., Fattorusso, E., Lanzotti, V., Motti, R., Simon, P.N., Dumontet, C., Di Pietro, A., 2004. Jatrophone diterpenes as modulators of multidrug resistance. advances of structure-activity relationships and discovery of the potent lead Pepluanin A. *J. Med. Chem.* 47 <https://doi.org/10.1021/jm030951y>.
- Costa-Lotufo, L.V., Cunha, G.M.A., Farias, P.A.M., Viana, G.S.B., Cunha, K.M.A., Pessoa, C., Moraes, M.O., Silveira, E.R., Gramosa, N.V., Rao, V.S.N., 2002. The cytotoxic and embryotoxic effects of kaurenoic acid, a diterpene isolated from *Copaifera langsdorffii* oleo-resin. *Toxicol.* 40 [https://doi.org/10.1016/S0041-0101\(02\)00128-9](https://doi.org/10.1016/S0041-0101(02)00128-9).
- D'Alesio, C., Bellese, G., Gagliani, M.C., Aiello, C., Grasselli, E., Marrocchi, G., Bisio, A., Tavella, S., Daniele, T., Cortese, K., Castagnola, P., 2017. Cooperative antitumor activities of carnosic acid and Trastuzumab in ERBB2+ breast cancer cells. *J. Exp. Clin. Cancer Research* 36. <https://doi.org/10.1186/s13046-017-0615-0>.
- Dauby, G., Zaiss, R., Blach-Overgaard, A., Catarino, L., Damen, T., Deblauwe, V., Dessen, S., Dransfield, J., Droissart, V., Duarte, M.C., Engledow, H., Fadeur, G., Figueira, R., Gereau, R.E., Hardy, O.J., Harris, D.J., De Heij, J., Janssens, S., Klomberg, Y., Ley, A.C., Mackinder, B.A., Meerts, P., Van De Poel, J.L., Sonké, B., Sosef, M.S.M., Stévant, T., Stoffelen, P., Svenning, J.C., Sepulchre, P., Van Der Burg, X., Wieringa, J.J., Couvreur, T.L.P., 2016. RAINBIO: a mega-database of tropical African vascular plants distributions. *PhytoKeys*. 74 <https://doi.org/10.3897/phytokeys.74.9723>.
- De Cedron, M.G., Laparra, J.M., Loria-Kohen, V., Molina, S., Moreno-Rubio, J., Montoya, J.J., Torres, C., Casado, E., Reglero, G., De Molina, A.R., 2019. Tolerability and safety of a nutritional supplement with potential as adjuvant in colorectal cancer therapy: a randomized trial in healthy volunteers. *Nutrients*. 11 <https://doi.org/10.3390/nu11092001>.
- de Oliveira, P.F., Munari, C.C., Nicoletta, H.D., Veneziani, R.C., Tavares, D.C., 2016. Manool, a *Salvia officinalis* diterpene, induces selective cytotoxicity in cancer cells. *Cytotechnology* 68 (5), 2139–2143. <https://doi.org/10.1007/s10616-015-9927-0>.
- Del Rosso, J.Q., 2016. Ingenol Mebutate Topical Gel A Status Report On Clinical Use Beyond Actinic Keratosis. *J. Clin. Aesthet. Dermatol.* 9 (11 Suppl 1), S3–S11.
- Denis, O., Richarh, K., Motlalepula, G.M., Youngmin, K., 2018. A review on the botanical aspects, phytochemical contents and pharmacological activities of *Warburgia ugandensis*. *J. Medicin. Plants Res.* 12 <https://doi.org/10.5897/jmpr2018.6626>.
- Domínguez-Martín, E.M., Díaz-Lanza, A.M., Faustino, C.M.C., 2019. Anticancer hybrid combinations: mechanisms of action, implications and future perspectives. *Curr. Pharm. Des.* 24 <https://doi.org/10.2174/1381612825666190110162529>.
- Domínguez-Martín, E.M., Magalhães, M., Efferth, T., Díaz-Lanza, A.M., Cabral, C., Rijo, P., 2023. Terpenes: a hope for glioblastoma patients. In: *New Insights Into Glioblastoma*, 227–269. <https://doi.org/10.1016/B978-0-323-99873-4.00014-1>.
- Efferth, T., Banerjee, M., Paul, N.W., Abdelatah, S., Arend, J., Elhassan, G., Hamdoun, S., Hamm, R., Hong, C., Kadioglu, O., Naß, J., Ochwangi, D., Ooko, E., Ozenver, N., Saeed, M.E., Schneider, M., Seo, E.J., Wu, C.F., Yan, G., Zeino, M., Zhao, Q., Abu-Darwish, M.S., Andersch, K., Alexie, G., Bessarab, D., Bhakta-Guha, D., Bolzani, V., Daput, E., Donenko, F.V., Efferth, M., Greten, H.J., Gunatilaka, L., Hussein, A.A., Karadeniz, A., Khalid, H.E., Kuete, V., Lee, I.S., Liu, L., Midiwo, J., Mora, R., Nakagawa, H., Ngassapa, O., Noysang, C., Omosa, L.K., Roland, F.H., Shahat, A.A., Saab, A., Saeed, E.M., Shan, L., Titinchi, S.J., 2016. Biopiracy of natural products and good bioprospecting practice. *Phytomedicine* 23 (2), 166–173. <https://doi.org/10.1016/j.phymed.2015.12.006>.
- Efferth, T., Xu, A.L., Lee, D.Y.W., 2019. Combining the wisdoms of traditional medicine with cutting-edge science and technology at the forefront of medical sciences. *Phytomedicine* 64, 153078. <https://doi.org/10.1016/j.phymed.2019.153078>.
- El-Huneidi, W., Bajbouj, K., Muhammad, J.S., Vinod, A., Shafarin, J., Khoder, G., Saleh, M.A., Taneera, J., Abu-Gharbieh, E., 2021. Carnosic acid induces apoptosis and inhibits akt/mTOR signaling in human gastric cancer cell lines. *Pharmaceuticals* 14. <https://doi.org/10.3390/ph14030230>.
- European Medicines Agency, 2020. EMA Suspend Picato as a Precaution While Review of Skin Cancer Risk Continues. *Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands*.
- European Medicines Agency, 2021. Yondelis : EPAR - Risk-Management-Plan Summary. *Domenico Scarlattilaan 6, 1083 HS, Amsterdam, The Netherlands*.
- Fagundes, T.R., Taciane da Silva Bortoleti, B., Tomiotto-Pellissier, F., Concato, V.M., Gonçalves, M.D., Arakawa, N.S., Miranda-Sapla, M.M., Panis, C., Pavanelli, W.R., 2022. Grandiflorenic acid from *Wedelia trilobata* plant induces apoptosis and autophagy cell death in breast adenocarcinoma (MCF7), lung carcinoma (A549), and hepatocellular carcinoma (HuH7.5) cell lines. *Toxicol.* 217. <https://doi.org/10.1016/j.toxicol.2022.08.006>.
- Farah, Adriana, 2012. Coffee Constituents. Wiley. <https://doi.org/10.1002/9781119949893>.
- Farah, A., 2012. Coffee constituents. Coffee: Emerging Health Effects and Disease Prevention. <https://doi.org/10.1002/9781119949893.ch2>.
- Farooqi, A.A., Attar, R., Uteuliyev, Y.S., Alaaeddine, N., de Sousa, D.P., Xu, B., Cho, W.C., 2020. The prowess of andrographolide as a natural weapon in the war against cancer. *Cancers*. <https://doi.org/10.3390/cancers12082159>.
- Fattahian, M., Ghanadian, M., Ali, Z., Khan, I.A., 2020. Jatrophone and rearranged jatrophone-type diterpenes: biogenesis, structure, isolation, biological activity and SARs (1984–2019). *Phytochem. Rev.* <https://doi.org/10.1007/s11101-020-09667-8>.
- Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., Bray, F., 2020. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency For Research on Cancer [WWW Document]. International Agency for Research on Cancer, Lyon, France.
- Fernández-Ochoa, Borrás-Linares, I., Pérez-Sánchez, A., Barrajón-Catalán, E., González-Álvarez, I., Arráez-Román, D., Micol, V., Segura-Carretero, A., 2017. Phenolic compounds in rosemary as potential source of bioactive compounds against colorectal cancer: in situ absorption and metabolism study. *J. Funct. Foods*. 33 <https://doi.org/10.1016/j.jff.2017.03.046>.
- Forest, F., Grenyer, R., Rouget, M., Davies, T.J., Cowling, R.M., Faith, D.P., Balmford, A., Manning, J.C., Procheş, Ş., Van Der Bank, M., Reeves, G., Hedderson, T.A.J., Savolainen, V., 2007. Preserving the evolutionary potential of floras in biodiversity hotspots. *Nature* 445. <https://doi.org/10.1038/nature05587>.
- Franco, Y.E.M., Okubo, M.Y., Torre, A.D., Paiva, P.P., Rosa, M.N., Silva, V.A.O., Reis, R. M., Ruiz, A.L.T.G., Imamura, P.M., de Carvalho, J.E., Longato, G.B., 2019. Coronarin D induces apoptotic cell death and cell cycle arrest in human glioblastoma cell line. *Molecules* 24. <https://doi.org/10.3390/molecules24244498>.
- Gao, Q., Liu, H., Yao, Y., Geng, L., Zhang, X., Jiang, L., Shi, B., Yang, F., 2015. Carnosic acid induces autophagic cell death through inhibition of the Akt/mTOR pathway in human hepatoma cells. *J. Appl. Toxicol.* 35 <https://doi.org/10.1002/jat.3049>.
- Gao, J., Zhang, Y., Liu, X., Wu, X., Huang, L., Gao, W., 2021. Triptolide: pharmacological spectrum, biosynthesis, chemical synthesis and derivatives. *Theranostics*. 11, 7199–7221. <https://doi.org/10.7150/thno.57745>.
- Gbedema, S.Y., Bayor, M.T., Annan, K., Wright, C.W., 2015. Clerodane diterpenes from *Polyalthia longifolia* (Sonn) Thw. var. pendula: potential antimalarial agents for drug resistant *Plasmodium falciparum* infection. *J. Ethnopharmacol.* 169 <https://doi.org/10.1016/j.jep.2015.04.014>.
- Giacomelli, C., Daniele, S., Natali, L., Iofrida, C., Flamini, G., Braca, A., Trincavelli, M.L., Martini, C., 2017. Carnosol controls the human glioblastoma stemness features through the epithelial-mesenchymal transition modulation and the induction of cancer stem cell apoptosis. *Sci. Rep.* 7 <https://doi.org/10.1038/s41598-017-15360-2>.
- Gill, B.A., Musili, P.M., Kurukura, S., Hassan, A.A., Goheen, J.R., Kress, W.J., Kuzmina, M., Pringle, R.M., Kartzin, T.R., 2019. Plant DNA-barcode library and community phylogeny for a semi-arid East African savanna. *Mol. Ecol. Resour.* 19 <https://doi.org/10.1111/1755-0998.13001>.
- Gonçalves, M.D., Bortoleti, B.T., da, S., Tomiotto-Pellissier, F., Concato, V.M., de Matos, R.L.N., Silva, T.F., Rodrigues, A.C.J., Carlotto, A.C.M., Costa, I.N., Lazarin-Bidóia, D., Miranda-Sapla, M.M., Pavanelli, W.R., Arakawa, N.S., Conchon-Costa, I., 2022. Grandiflorenic acid isolated from *Sphagneticola trilobata* against *Trypanosoma cruzi*: toxicity, mechanisms of action and immunomodulation. *Toxicol. in Vitro* 78. <https://doi.org/10.1016/j.tiv.2021.105267>.
- Gong, G., Shen, Y.L., Lan, H.Y., Jin, J.M., An, P., Zhang, L.J., Chen, L.L., Peng, W., Luan, X., Zhang, H., 2021. The Cyr61 is a potential target for rotundifuran, a natural

- labdane-type diterpene from *Vitex trifolia* L., to trigger apoptosis of cervical cancer cells. *Oxid. Med. Cell Longev.* 2021 <https://doi.org/10.1155/2021/6677687>.
- González-Vallinas, M., Molina, S., Vicente, G., De La Cueva, A., Vargas, T., Santoyo, S., García-Risco, M.R., Fornari, T., Reglero, G., Ramírez De Molina, A., 2013. Antitumor effect of 5-fluorouracil is enhanced by rosemary extract in both drug sensitive and resistant colon cancer cells. *Pharmacol. Res.* 72 <https://doi.org/10.1016/j.phrs.2013.03.010>.
- González-Vallinas, M., Molina, S., Vicente, G., Sánchez-Martínez, R., Vargas, T., García-Risco, M.R., Fornari, T., Reglero, G., Ramírez de Molina, A., 2014a. Modulation of estrogen and epidermal growth factor receptors by rosemary extract in breast cancer cells. *Electrophoresis* 35. <https://doi.org/10.1002/elps.201400011>.
- González-Vallinas, M., Molina, S., Vicente, G., Zarza, V., Martín-Hernández, R., García-Risco, M.R., Fornari, T., Reglero, G., De Molina, A.R., 2014b. Expression of MicroRNA-15b and the glycosyltransferase GCNT3 correlates with antitumor efficacy of rosemary diterpenes in colon and pancreatic cancer. *PLoS ONE* 9. <https://doi.org/10.1371/journal.pone.0098556>.
- González-Vallinas, M., Reglero, G., Ramírez De Molina, A., 2015. Rosemary (*Rosmarinus officinalis* L.) extract as a potential complementary agent in anticancer therapy. *Nutr. Cancer.* <https://doi.org/10.1080/01635581.2015.1082110>.
- Grkovic, T., Evans, J.R., Akee, R.K., Guo, L., Davis, M., Jato, J., Grothaus, P.G., Ahalt-Gotholm, M., Hollingshead, M., Collins, J.M., Newman, D.J., O'Keefe, B.R., 2019. Erythroforins D and E, two new cassaine-type diterpenes from *Erythrophleum suaveolens*. *Bioorg. Med. Chem. Lett.* 29 <https://doi.org/10.1016/j.bmcl.2018.12.019>.
- Guo, X., Bai, X., Li, L., Li, J., Wang, H., 2018. Forskolin protects against cisplatin-induced ototoxicity by inhibiting apoptosis and ROS production. *Biomed. Pharmacother.* 99 <https://doi.org/10.1016/j.biopha.2018.01.080>.
- Gupta, A.K., Paquet, M., 2013. Ingenol mebutate: a promising treatment for actinic keratoses and nonmelanoma skin cancers. *J. Cutan. Med. Surg.* <https://doi.org/10.2310/7750.2012.12050>.
- Ha, M.T., Tran, M.H., Phuong, T.T., Kim, J.A., Woo, M.H., Choi, J.S., Lee, S., Lee, J.H., Lee, H.K., Min, B.S., 2017. Cytotoxic and apoptosis-inducing activities against human lung cancer cell lines of cassaine diterpenoids from the bark of *Erythrophleum fordii*. *Bioorg. Med. Chem. Lett.* 27 <https://doi.org/10.1016/j.bmcl.2017.05.006>.
- Han, J., Chen, Y., Bao, L., Yang, X., Liu, D., Li, S., Zhao, F., Liu, H., 2013. Anti-inflammatory and cytotoxic cyathane diterpenoids from the medicinal fungus *Cyathus africanus*. *Fitoterapia* 84. <https://doi.org/10.1016/j.fitote.2012.10.001>.
- Han, S., Li, X., Xia, Y., Yu, Z., Cai, N., Malwal, S.R., Han, X., Oldfield, E., Zhang, Y., 2019. Farnesyl pyrophosphate synthase as a target for drug development: discovery of natural-product-derived inhibitors and their activity in pancreatic cancer cells. *J. Med. Chem.* 62 <https://doi.org/10.1021/acs.jmedchem.9b01405>.
- Hao, D.-C., Ge, G.-B., Xiao, P.-G., 2017. Anticancer drug targets of salvia phytometabolites: chemistry, Biology and Omics. *Curr. Drug Targets* 19. <https://doi.org/10.2174/1389450117666161207141020>.
- He, L., Han, J., Li, B., Huang, L., Ma, K., Chen, Q., Liu, X., Bao, L., Liu, H., 2016. Identification of a new cyathane diterpene that induces mitochondrial and autophagy-dependent apoptosis and shows a potent *in vivo* anti-colorectal cancer activity. *Eur. J. Med. Chem.* 111, 183–192. <https://doi.org/10.1016/j.ejmech.2016.01.056>.
- Heinrich, M., Lardos, A., Leonti, M., Weckerle, C., Willcox, M., Applequist, W., Ladio, A., Lin Long, C., Mukherjee, P., Stafford, G., 2018. Best practice in research: consensus statement on ethnopharmacological field studies – ConSEFS. *J. Ethnopharmacol.* <https://doi.org/10.1016/j.jep.2017.08.015>.
- Hossain, M.S., Urbi, Z., Sule, A., Rahman, K.M.H., 2014. *Andrographis paniculata* (Burm. f.) Wall. ex Nees: a review of ethnobotany, phytochemistry, and pharmacology. *Sci. World J.* <https://doi.org/10.1155/2014/274905>.
- Hu, R., Gao, J., Rozimamat, R., Aisa, H.A., 2018. Jatropane diterpenoids from *Euphorbia sororia* as potent modulators against P-glycoprotein-based multidrug resistance. *Eur. J. Med. Chem.* 146, 157–170. <https://doi.org/10.1016/j.ejmech.2018.01.027>.
- Hueso-Falcón, I., Girón, N., Velasco, P., Amaro-Luis, J.M., Ravelo, A.G., Heras, B.de las, Hortelano, S., Estevez-Braun, A., 2010. Synthesis and induction of apoptosis signaling pathway of ent-kaurane derivatives. *Bioorg. Med. Chem.* 18 <https://doi.org/10.1016/j.bmc.2009.11.064>.
- Huo, J.F., Hu, T.X., Dong, Y.L., Zhao, J.Z., Liu, X.J., Li, L.L., Zhang, X.Y., Li, Y.F., Liu, H. M., Ke, Y., Wang, C., 2020. Synthesis and *in vitro* and *in vivo* biological evaluation of novel derivatives of flexicaulin A as antiproliferative agents. *Eur. J. Med. Chem.* 208 <https://doi.org/10.1016/j.ejmech.2020.112789>.
- Hussein, A., 2018. Chemistry of South African lamiaceae: structures and biological activity of terpenoids. *Terpenes and Terpenoids.* <https://doi.org/10.5772/intechopen.77399>.
- Islam, M.T., Ali, E.S., Uddin, S.J., Islam, M.A., Shaw, S., Khan, I.N., Saravi, S.S.S., Ahmad, S., Rehman, S., Gupta, V.K., Gáman, M.A., Gáman, A.M., Yeles, S., Das, A.K., de Castro e Sousa, J.M., de Moura Dantas, S.M.M., Rolim, H.M.L., de Carvalho Melo-Cavalcante, A.A., Mubarak, M.S., Yarla, N.S., Shilpi, J.A., Mishra, S.K., Atanasov, A. G., Kamal, M.A., 2018. Andrographolide, a diterpene lactone from *Andrographis paniculata* and its therapeutic promises in cancer. *Cancer Lett.* <https://doi.org/10.1016/j.canlet.2018.01.074>.
- Isyaka, S.M., Langat, M.K., Mas-Claret, E., Mbala, B.M., Mvingu, B.K., Mulholland, D.A., 2020. Ent-abietane and ent-pimarane diterpenoids from *Croton mubungu* (Euphorbiaceae). *Phytochemistry* 170. <https://doi.org/10.1016/j.phytochem.2019.112217>.
- Iwamoto, H., Izumi, K., Natsagdorj, A., Naito, R., Makino, T., Kadomoto, S., Hiratsuka, K., Shigehara, K., Kadono, Y., Narimoto, K., Saito, Y., Nakagawa-Goto, K., Mizokami, A., 2019. Coffee diterpenes kahweol acetate and cafestol synergistically inhibit the proliferation and migration of prostate cancer cells. *Prostate* 79. <https://doi.org/10.1002/pros.23753>.
- Jiang, D., Xu, J., Liu, S., Nasser, M.I., Wei, W., Mao, T., Liu, X., Zou, X., Li, J., Li, X., 2021. Rosmanol induces breast cancer cells apoptosis by regulating PI3K/AKT and STAT3/JAK2 signaling pathways. *Oncol. Lett.* 22 <https://doi.org/10.3892/ol.2021.12892>.
- Jiang, S., Qiu, Y., Wang, Z., Ji, Y., Zhang, X., Yan, X., Zhan, Z., 2021. Carnosic acid induces antiproliferation and anti-metastatic property of esophageal cancer cells via MAPK signaling pathways. *J. Oncol.* 2021 <https://doi.org/10.1155/2021/4451533>.
- Jing, W., Zhang, X.X., Zhou, H., Wang, Y., Yang, M., Long, L., Gao, H., 2019. Naturally occurring cassane diterpenoids (CAs) of *Caesalpinia*: a systematic review of its biosynthesis, chemistry and pharmacology. *Fitoterapia* 134, 226–249. <https://doi.org/10.1016/j.fitote.2019.02.023>.
- Kandanur, S.G.S., Tamang, N., Golakoti, N.R., Nanduri, S., 2019. Andrographolide: a natural product template for the generation of structurally and biologically diverse diterpenes. *Eur. J. Med. Chem.* <https://doi.org/10.1016/j.ejmech.2019.05.022>.
- Kasagana, V.N., Karumuri, S.S., 2011. Conservation of medicinal plants (past, present & future trends). *J. Pharm. Sci. Res.* 3.
- Kembai, D., Peter, X., Langat, M., Tembu, J., 2020. A Review of the ethnomedicinal uses, biological activities, and triterpenoids of euphorbia species. *Molecules.* <https://doi.org/10.3390/molecules25174019>.
- Kew Royal Botanic Gardens, n.d. Plants of the World Online [WWW Document]. <http://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:347643-1>.
- Khalifa, S.A.M., Elias, N., Farag, M.A., Chen, L., Saeed, A., Hegazy, M.E.F., Moustafa, M. S., El-Wahed, A.A., Al-Mousawi, S.M., Musharraf, S.G., Chang, F.R., Iwasaki, A., Suenaga, K., Alajlani, M., Göransson, U., El-Seedi, H.R., 2019. Marine natural products: a source of novel anticancer drugs. *Mar. Drugs.* <https://doi.org/10.3390/md17090491>.
- Kim, E.J., Kang, J.I.I., Tung, N.H., Kim, Y.H., Hyun, J.W., Koh, Y.S., Chang, W.Y., Yoo, E. S., Kang, H.K., 2016. The effect of (1S,2S,3E,7E,11E)-3,7,11,15-cembratetraen-17,2-olide (LS-1) from *Lobophyllum* sp. On the apoptosis induction of SNU-C5 human colorectal cancer cells. *Biomol. Ther. (Seoul)* 24. <https://doi.org/10.4062/biomolther.2016.023>.
- Kim, H.J., Seo, B.G., Kim, K.D., Yoo, J., Lee, Joon Hee, Min, B.S., Lee, Jeong Hyung, Hwangbo, C., 2020. C5, a cassaine diterpenoid amine, induces apoptosis via the extrinsic pathways in human lung cancer cells and human lymphoma cells. *Int. J. Mol. Sci.* 21 <https://doi.org/10.3390/ijms21041298>.
- Kiss, T., Mácsai, L., Csupor, D., Datki, Z.L., 2017. *In vivo* screening of diterpene alkaloids using bdelloid rotifer assays. *Acta Biol. Hung.* 68, 443–452. <https://doi.org/10.1556/118.68.2017.4.9>.
- Kuete, V., Efferth, T., 2015. African flora has the potential to fight multidrug resistance of cancer. *Biomed. Res. Int.* <https://doi.org/10.1155/2015/914813>.
- Kumar, G., Singh, D., Tali, J.A., Dheer, D., Shankar, R., 2020. Andrographolide: chemical modification and its effect on biological activities. *Bioorg. Chem.* 95, 103511 <https://doi.org/10.1016/j.bioorg.2019.103511>.
- López-Jiménez, A., García-Caballero, M., Medina, M.A., Quesada, A.R., 2013. Anti-angiogenic properties of carnosol and carnosic acid, two major dietary compounds from rosemary. *Eur. J. Nutr.* 52 <https://doi.org/10.1007/s00394-011-0289-x>.
- Lai, K.M., Wang, J.H., Lin, S.C., Wen, Y., Wu, C.L., Su, J.H., Chen, C.C., Lin, C.C., 2022. Crassolide induces G2/M cell cycle arrest, apoptosis, and autophagy in human lung cancer cells via ROS-Mediated ER stress pathways. *Int. J. Mol. Sci.* 23 <https://doi.org/10.3390/ijms23105624>.
- Lefranc, F., Koutsaviti, A., Ioannou, E., Kornienko, A., Roussis, V., Kiss, R., Newman, D., 2019. Algae metabolites: from *in vitro* growth inhibitory effects to promising anticancer activity. *Nat. Prod. Rep.* <https://doi.org/10.1039/c8np00057c>.
- Li, S.F., Yu, X.Q., Li, Y.L., Bai, M., Lin, B., Yao, G.D., Song, S.J., 2021. Vibsane-type diterpenoids from *Viburnum odoratissimum* and their cytotoxic activities. *Bioorg. Chem.* 106 <https://doi.org/10.1016/j.bioorg.2020.104498>.
- Li, M., Zhou, Z.P., Yuan, Z.F., Zhao, Q.S., 2022. Vibsane-type diterpenoids: structures, derivatives, bioactivities, and synthesis. *Chem. Biodivers.* <https://doi.org/10.1002/cbdv.202100861>.
- Liang, X., Gao, Y., Luan, S., 2018. Two decades of advances in diterpenoid alkaloids with cytotoxicity activities. *RSC Adv.* 8, 23937–23946. <https://doi.org/10.1039/c8ra03911a>.
- Lima, C.S., Spindola, D.G., Bechara, A., Garcia, D.M., Palmeira-dos-Santos, C., Peixoto-da-Silva, J., Erustes, A.G., Michelin, L.F.G., Pereira, G.J.S., Smaili, S.S., Paredes-Gamero, E., Calgarotto, A.K., Oliveira, C.R., Bincioletto, C., 2017. Cafestol, a diterpene molecule found in coffee, induces leukemia cell death. *Biomed. Pharmacother.* 92 <https://doi.org/10.1016/j.biopha.2017.05.109>.
- Lin, Z., Guo, Y., Gao, Y., Wang, S., Wang, X., Xie, Z., Niu, H., Chang, W., Liu, L., Yuan, H., Lou, H., 2015. ent-kaurane diterpenoids from Chinese liverworts and their antitumor activities through Michael addition as detected *in situ* by a fluorescence probe. *J. Med. Chem.* 58 <https://doi.org/10.1021/acs.jmedchem.5b00208>.
- Lin, H., Jackson, G.A., Lu, Y., Drenkhahn, S.K., Brownstein, K.J., Starkey, N.J., Lamberson, W.R., Fritsche, K.L., Mossine, V.V., Besch-Williford, C.L., Folk, W.R., Zhang, Y., Lubahn, D.B., 2016. Inhibition of Gli/hedgehog signaling in prostate cancer cells by “cancer bush” *Sutherlandia frutescens* extract. *Cell Biol. Int.* 40 <https://doi.org/10.1002/cbin.10544>.
- Lin, K.I., Lin, C.C., Kuo, S.M., Lai, J.C., Wang, Y.Q., You, H.L., Hsu, M.L., Chen, C.H., Shiu, L.Y., 2018. Carnosic acid impedes cell growth and enhances anticancer effects of carmustine and lomustine in melanoma. *Biosci. Rep.* 38 <https://doi.org/10.1042/BSR20180005>.
- Linder, H.P., 2014. The evolution of African plant diversity. *Front. Ecol. Evol.* 2 <https://doi.org/10.3389/fevo.2014.00038>.
- Lindsell, J.A., Klop, E., Siaka, A.M., 2011. The impact of civil war on forest wildlife in West Africa: Mammals in Gola Forest. *Sierra Leone. ORYX* 45. <https://doi.org/10.1017/S0030605310000347>.

- Ling, T., Lang, W.H., Craig, J., Potts, M.B., Budhraj, A., Opferman, J., Bollinger, J., Maier, J., Marsico, T.D., Rivas, F., 2019. Studies of Jatrogossone A as a reactive oxygen species inducer in cancer cellular models. *J. Nat. Prod.* 82 <https://doi.org/10.1021/acs.jnatprod.8b01087>.
- Liu, C., Lee, W.C., Huang, B.M., Chia, Y.C., Chen, Yu Chi, Chen, Yung Chia, 2017. 16-Hydroxycyclohexa-3, 13-dien-15, 16-olide inhibits the proliferation and induces mitochondrial-dependent apoptosis through Akt, mTOR, and MEK-ERK pathways in human renal carcinoma cells. *Phytomedicine* 36. <https://doi.org/10.1016/j.phymed.2017.09.021>.
- Liu, S.N., Hu, J., Tan, S.H., Wang, Q., Xu, J., Wang, Y., Yuan, Y., Gu, Q., 2017. Ent-Rosane diterpenoids from *Euphorbia milii* showing an Epstein-Barr virus lytic replication assay. *RSC Adv.* 7 <https://doi.org/10.1039/c7ra08877a>.
- LIU, W., WU, T.C., HONG, D.M., HU, Y., FAN, T., GUO, W.J., XU, Q., 2018. Carnosic acid enhances the anti-lung cancer effect of cisplatin by inhibiting myeloid-derived suppressor cells. *Chin. J. Nat. Med.* 16 [https://doi.org/10.1016/S1875-5364\(18\)30132-8](https://doi.org/10.1016/S1875-5364(18)30132-8).
- Liu, Y.T., Hsieh, M.J., Lin, J.T., Chen, G., Lin, C.C., Lo, Y.S., Chuang, Y.C., Hsi, Y.T., Chen, M.K., Chou, M.C., 2019. Coronarin D induces human oral cancer cell apoptosis through upregulate JNK1/2 signaling pathway. *Environ. Toxicol.* 34 <https://doi.org/10.1002/tox.22705>.
- Liu, Y., Chen, P., Qi, D., Chen, L., 2022. Glaucoalyxin A Inhibits the Malignancies of Gastric Cancer Cells by Downregulating MDM2 and RNF6 via MiR-3658 and the SMG1-UPF mRNA Decay Pathway. *Front. Oncol.* 12 <https://doi.org/10.3389/fonc.2022.871169>.
- Lizarte Neto, F.S., Tirapelli, D.P.C., Ambrosio, S.R., Tirapelli, C.R., Oliveira, F.M., Novais, P.C., Peria, F.M., Oliveira, H.F., Carloti Junior, C.G., Tirapelli, L.F., 2013. Kaurene diterpene induces apoptosis in U87 human malignant glioblastoma cells by suppression of anti-apoptotic signals and activation of cysteine proteases. *Braz. J. Med. Biol. Res.* 46 <https://doi.org/10.1590/1414-431x20121423>.
- Loh, S.H., Tsai, Y.T., Huang, S.F., Yu, T.C., Kuo, P.C., Chao, S.C., Chou, M.F., Tsai, C.S., Lee, S.P., 2021. Effects of andrographolide on intracellular pH regulation, cellular migration, and apoptosis in human cervical cancer cells. *Cancers* 12. <https://doi.org/10.3390/cancers12020387>.
- Lu, C.C., Huang, W.S., Lee, K.F., Lee, K.C., Hsieh, M.C., Huang, C.Y., Lee, L.Y., Lee, B.O., Teng, C.C., Shen, C.H., Tung, S.Y., Kuo, H.C., 2016. Inhibitory effect of Erinacines A on the growth of DLD-colorectal cancer cells is induced by generation of reactive oxygen species and activation of p70S6K and p21. *J. Funct. Foods* 21, 474–484. <https://doi.org/10.1016/j.jff.2015.12.031>.
- Lu, S., Li, Yiwei, Shen, Q., Zhang, W., Gu, X., Ma, M., Li, Yiming, Zhang, L., Liu, X., Zhang, X., 2021. Carnosol and its analogues attenuate muscle atrophy and fat lipolysis induced by cancer cachexia. *J. Cachexia Sarcopenia Muscle* 12. <https://doi.org/10.1002/jcsm.12710>.
- Makino, T., Izumi, K., Hiratsuka, K., Kano, H., Shimada, T., Nakano, T., Kadomoto, S., Naito, R., Iwamoto, H., Yaegashi, H., Shigehara, K., Kadono, Y., Nakata, H., Saito, Y., Nakagawa-Goto, K., Sakai, N., Iwata, Y., Wada, T., Mizokami, A., 2021. Anti-proliferative and anti-migratory properties of coffee diterpenes kahweol acetate and cafestol in human renal cancer cells. *Sci. Rep.* 11, 1–10. <https://doi.org/10.1038/s41598-020-80302-4>.
- Mantaj, J., Rahman, S.M.A., Bokshi, B., Hasan, C.M., Jackson, P.J.M., Parsons, R.B., Rahman, K.M., 2015. Crispene E, a cis-clerodane diterpene inhibits STAT3 dimerization in breast cancer cells. *Org. Biomol. Chem.* 13 <https://doi.org/10.1039/c5ob00052a>.
- Marshall, C.A.M., Wieringa, J.J., Hawthorne, W.D., 2016. Bioquality Hotspots in the Tropical African Flora. *Curr. Biol.* 26 <https://doi.org/10.1016/j.cub.2016.09.045>.
- Mbaveng, A.T., Kuete, V., Efferth, T., 2017. Potential of Central, Eastern and Western Africa Medicinal Plants for Cancer Therapy: Spotlight on Resistant Cells and Molecular Targets. *Front. Pharmacol.* 8, 343. <https://doi.org/10.3389/fphar.2017.00343>.
- McKeon, T.A., 2016. Emerging industrial oil crops. *Ind.Oil Crops* 275–341. <https://doi.org/10.1016/B978-1-893997-98-1.00011-7>.
- Mingou, P.A.B., Gueye, M., Abotsi, K.E., Bayet, T., Cambier, C., Rouhan, G., 2021. Three new records of fern species (Polypodiopsida) in senegal, from diñdefelo falls, kedougou region. *Check. List.* 17 <https://doi.org/10.15560/17.3.923>.
- Mizuno, C.S., Souza, A.B., Tekwani, B.L., Ambrósio, S.R., Veneziani, R.C.S., 2015. Synthesis and biological evaluation of polyalthic acid derivatives for the treatment of neglected diseases. *Bioorg. Med. Chem. Lett.* 25 <https://doi.org/10.1016/j.bmcl.2015.10.062>.
- Moeenfar, M., Alves, A., 2020. New trends in coffee diterpenes research from technological to health aspects. *Food Res. Int.* <https://doi.org/10.1016/j.foodres.2020.109207>.
- Moeenfar, M., Cortez, A., Machado, V., Costa, R., Luís, C., Coelho, P., Soares, R., Alves, A., Borges, N., Santos, A., 2016. Anti-angiogenic properties of cafestol and kahweol palmitate diterpene esters. *J. Cell Biochem.* 2748–2756. <https://doi.org/10.1002/jcb.25573>.
- Morelli, C.L., Mahrous, M., Belgacem, M.N., Branciforti, M.C., Bretas, R.E.S., Bras, J., 2015. Natural copaiba oil as antibacterial agent for bio-based active packaging. *Ind. Crops. Prod.* 70, 134–141. <https://doi.org/10.1016/j.indcrop.2015.03.036>.
- Moshiashvili, G., Tabatadze, N., Mshvildadze, V., 2020. The genus *Daphne*: a review of its traditional uses, phytochemistry and pharmacology. *Fitoterapia*. <https://doi.org/10.1016/j.fitote.2020.104540>.
- Moudi, M., Go, R., Yien, C.Y.S., Nazre, M., 2013. Vinca alkaloids. *Int. J. Prev. Med.* <https://doi.org/10.2165/00128415-200711380-00080>.
- Moyo, M., Aremu, A.O., Van Staden, J., 2015. Medicinal plants: an invaluable, dwindling resource in sub-Saharan Africa. *J. Ethnopharmacol.* 174 <https://doi.org/10.1016/j.jep.2015.04.034>.
- Nabatchian, F., Moradi, A., Aghaei, M., Ghanadian, M., Jafari, S.M., Tabesh, S., 2017. New 6(17)-epoxylathyrane diterpene: aellinane from *Euphorbia aellenii* induces apoptosis via mitochondrial pathway in ovarian cancer cell line. *Toxicol. Mech. Methods* 27. <https://doi.org/10.1080/15376516.2017.1347735>.
- National Library of Medicine, n.d. Clinicaltrials.gov [WWW Document]. <https://clinicaltrials.gov/>.
- Nature, 2023. Nature Index 2023 Tables: Countries/Territories - Biological Sciences [WWW Document]. <https://www.nature.com/nature-index/annual-tables/2023/country/biological-sciences/all>.
- Neto, S., Duarte, N., Pedro, C., Spengler, G., Molnár, J., Ferreira, M.J.U., 2019. Effective MDR reversers through phytochemical study of *Euphorbia boetica*. *Phytochem. Anal.* 30 <https://doi.org/10.1002/pca.2841>.
- Neumann, J., Yang, Y., Köhler, R., Giais, M., Witzens-Harig, M., Liu, D., Krammer, P.H., Lin, W., Li-Weber, M., 2015. Mangrove dolabrane-type of diterpenes tagalsins suppresses tumor growth via ROS-mediated apoptosis and ATM/ATR-Chk1/Chk2-regulated cell cycle arrest. *Int. J. Cancer* 137. <https://doi.org/10.1002/ijc.29629>.
- Ntungwe, E.N., Stojanov, S.J., Duarte, N.M., Candeias, N.R., Díaz-Lanza, A.M., Vágvolgyi, M., Hunyadi, A., Pešić, M., Rijo, P., 2022. C20- nor-abietane and three abietane diterpenoids from *Plectranthus mutabilis* leaves as P-glycoprotein modulators. *ACS. Med. Chem. Lett.* 13 <https://doi.org/10.1021/acsmchemlett.1c00711>.
- Oh, S.H., Hwang, Y.P., Choi, J.H., Jin, S.W., Lee, G.H., Han, E.H., Chung, Y.H., Chung, Y. C., Jeong, H.G., 2018. Kahweol inhibits proliferation and induces apoptosis by suppressing fatty acid synthase in HER2-overexpressing cancer cells. *Food Chem. Toxicol.* 121 <https://doi.org/10.1016/j.fct.2018.09.008>.
- Okaiyeto, K., Oguntibeju, O.O., 2021. African herbal medicines: adverse effects and cytotoxic potentials with different therapeutic applications. *Int. J. Environ. Res. Public Health*. <https://doi.org/10.3390/ijerph18115988>.
- Okoye, T.C., Akah, P.A., Okoli, C.O., Ezike, A.C., Omeje, E.O., Odoh, U.E., 2012. Antimicrobial Effects of a Lipophilic Fraction and Kaurenoic Acid Isolated from the Root Bark Extracts of *Annona senegalensis*. *Evid.-Based Complement. Altern. Med.* 2012 <https://doi.org/10.1155/2012/831327>.
- Panizza, B.J., de Souza, P., Cooper, A., Roohullah, A., Karapetis, C.S., Lickliter, J.D., 2019. Phase I dose-escalation study to determine the safety, tolerability, preliminary efficacy and pharmacokinetics of an intratumoral injection of tigilanol tiglate (EBC-46). *EBioMedicine* 50. <https://doi.org/10.1016/j.ebiom.2019.11.037>.
- Park, S.Y., Song, H., Sung, M.K., Kang, Y.H., Lee, K.W., Park, J.H.Y., 2014. Carnosic acid inhibits the Epithelial-Mesenchymal transition in B16F10 Melanoma Cells: a possible mechanism for the inhibition of cell Migration. *Int. J. Mol. Sci.* 15 <https://doi.org/10.3390/ijms150712698>.
- Park, G.H., Song, H.M., Jeong, J.B., 2016. The coffee diterpene kahweol suppresses the cell proliferation by inducing cyclin D1 proteasomal degradation via ERK1/2, JNK and GSK3β-dependent threonine-286 phosphorylation in human colorectal cancer cells. *Food Chem. Toxicol.* 95 <https://doi.org/10.1016/j.fct.2016.07.008>.
- Park, G.H., Song, H.M., Jeong, J.B., 2017. Kahweol from coffee induces apoptosis by upregulating activating transcription factor 3 in human colorectal cancer cells. *Biomol. Ther.* 25, 337–343. <https://doi.org/10.4062/biomolther.2016.114>.
- Patel, P.D., Alghareeb, R., Hussain, A., Maheshwari, M.V., Khalid, N., 2022. The association of epstein-barr virus with cancer. *Cureus*. <https://doi.org/10.7759/cureus.26314>.
- Peng, Y., Wang, Y., Tang, N., Sun, D., Lan, Y., Yu, Z., Zhao, X., Feng, L., Zhang, B., Jin, L., Yu, F., Ma, X., Lv, C., 2018. Andrographolide inhibits breast cancer through suppressing COX-2 expression and angiogenesis via inactivation of p300 signaling and VEGF pathway. *J. Exp. Clinical Cancer Research* 37. <https://doi.org/10.1186/s13046-018-0926-9>.
- Peterson, H., Luke, J., 2021. Ingenol Mebutate. *J. Dermatol. Nurses Assoc.* 13 <https://doi.org/10.1097/JDN.0000000000000587>.
- Petiwal, S.M., Johnson, J.J., 2015. Diterpenes from rosemary (*Rosmarinus officinalis*): defining their potential for anti-cancer activity. *Cancer Lett.* <https://doi.org/10.1016/j.canlet.2015.07.005>.
- Phan, N.D., Omar, A.M., Sun, S., Maneenet, J., Dibwe, D.F., Sato, M., Kalauni, S.K., Toyooka, N., Fujii, T., Awale, S., 2022. Abietane diterpenes from *Abies spectabilis* and their anti-pancreatic cancer activity against the MIA PaCa-2 cell line. *Bioorg. Med. Chem. Lett.* 66 <https://doi.org/10.1016/j.bmcl.2022.128723>.
- Piel, J., Butzke, D., Fusetani, N., Hui, D., Platzer, M., Wen, G., Matsunaga, S., 2005. Exploring the chemistry of uncultivated bacterial symbionts: antitumor polyketides of the Pederin family. *J. Nat. Prod.* <https://doi.org/10.1021/np049612d>.
- Popoola, O.K., Marnewick, J.L., Iwuoha, E.I., Hussein, A.A., 2023. Methoxylated Flavonols and ent-Kaurane Diterpenes from the South African *Helichrysum rutilans* and Their Cosmetic Potential. *Plants* 12. <https://doi.org/10.3390/plants12152870>.
- Pusztai, R., Ferreira, M.J.U., Duarte, N., Engi, H., Molnar, J., 2007. Macrocyclic lathyrane diterpenes as antitumor promoters. *Anticancer Res.* 27.
- Qasem, A.M.A., Zeng, Z., Rowan, M.G., Blagbrough, I.S., 2021. Norditerpenoid alkaloids from *Aconitum* and *Delphinium*: structural relevance in medicine, toxicology, and metabolism. *Nat. Prod. Rep.* 39 <https://doi.org/10.1039/d1np00029b>.
- Qiu, S., Wu, X., Liao, H., Zeng, X., Zhang, S., Lu, X., He, X., Zhang, X., Ye, W., Wu, H., Zhu, X., 2017. Pteisolic acid G, a novel ent-kaurane diterpenoid, inhibits viability and induces apoptosis in human colorectal carcinoma cells. *Oncol. Lett.* 14, 5540–5548. <https://doi.org/10.3892/ol.2017.6889>.
- Ravera, S., Esposito, A., Degan, P., Caicci, F., Manni, L., Liguori, A., Bisio, A., Iobbi, V., Schito, A., Traverso, C.E., Panfoli, I., 2021. The diterpene Manool extracted from *Salvia tingitana* lowers free radical production in retinal rod outer segments by inhibiting the extramitochondrial F1Fo ATP synthase. *Cell Biochem. Funct.* 39, 528–535. <https://doi.org/10.1002/cbf.3618>.
- Reis, M., Paterna, A., Ferreira, M., 2012. Phytochemical investigations of *Euphorbia piscatoria*. *Planta Med.* 78 <https://doi.org/10.1055/s-0032-1321070>.

- Reis, M., Ferreira, R.J., Santos, M.M.M., Dos Santos, D.J.V.A., Molnár, J., Ferreira, M.J.U., 2013. Enhancing macrocyclic diterpenes as multidrug-resistance reversers: structure-activity studies on jolkinol D derivatives. *J. Med. Chem.* 56 <https://doi.org/10.1021/jm301441w>.
- Reis, M.A., Paterna, A., Ferreira, R.J., Lage, H., Ferreira, M.J.U., 2014. Macrocyclic diterpenes resensitizing multidrug resistant phenotypes. *Bioorg. Med. Chem.* 22 <https://doi.org/10.1016/j.bmc.2014.05.006>.
- Reis, M.A., Ahmed, O.B., Spengler, G., Molnár, J., Lage, H., Ferreira, M.J.U., 2016. Jatrophone diterpenes and cancer multidrug resistance - ABCB1 efflux modulation and selective cell death induction. *Phytomedicine* 23. <https://doi.org/10.1016/j.phymed.2016.05.007>.
- Reis, M.A., Ahmed, O.B., Spengler, G., Molnár, J., Lage, H., Ferreira, M.J.U., 2017. Exploring Jolkinol D derivatives to overcome multidrug resistance in cancer. *J. Nat. Prod.* 80 <https://doi.org/10.1021/acs.jnatprod.6b01084>.
- Rocha, S.M.M.da, Cardoso, P.C.dos S., Bahia, M.de O., Pessoa, C.do Ó., Soares, P.C., Rocha, S.M.da, Burbano, R.M.R., Rocha, C.A.M.da, 2019. Effect of the kaurenoic acid on genotoxicity and cell cycle progression in cervical cancer cells lines. *Toxicol. in Vitro* 57. <https://doi.org/10.1016/j.tiv.2019.02.022>.
- Saito, T., Abe, D., Nogata, Y., 2015. Coffee diterpenes potentiate the cytolytic activity of KHYG-1 NK leukemia cells. *Food Sci Technol Res* 21. <https://doi.org/10.3136/fstr.21.281>.
- Sarwar, M.S., Xia, Y.X., Liang, Z.M., Tsang, S.W., Zhang, H.J., 2020. Mechanistic pathways and molecular targets of plant-derived anticancer ent-kaurene diterpenes. *BioMolecules* 10, 1–17. <https://doi.org/10.3390/biom10010144>.
- Seo, H.Y., Kim, M.K., Lee, S.H., Hwang, J.S., Park, K.G., Jang, B.K., 2018. Kahweol ameliorates the liver inflammation through the inhibition of NF- κ B and STAT3 activation in primary kupffer cells and primary hepatocytes. *Nutrients* 10. <https://doi.org/10.3390/nu10070863>.
- Seo, H.Y., Lee, S.H., Lee, J.H., Hwang, J.S., Kim, M.K., Jang, B.K., 2020. Kahweol activates the Nrf2/HO-1 pathway by decreasing Keap1 expression independently of p62 and autophagy pathways. *PLoS ONE* 15. <https://doi.org/10.1371/journal.pone.0240478>.
- Seo, H.Y., Lee, S.H., Lee, J.H., Lee, J.H., Lee, J.H., Lee, J.H., 2021. Kahweol induces apoptosis in hepatocellular carcinoma cells by inhibiting the Src/mTOR/STAT3 signaling pathway. *Int. J. Mol. Sci.* 22 <https://doi.org/10.3390/ijms221910509>.
- Sharifi, S., Mostafaei, P.G., Moradi, A.M., Givianrad, M.H., Niknejad, H., 2018. Inducing apoptosis of cancer cells using sea pen virgularia gustaviana extract which is comparable to cambrane diterpene sarcophine. *Iran. J. Pharm. Res.* 17.
- Shen, Y., Liang, W.J., Shi, Y.N., Kennelly, E.J., Zhao, D.K., 2020. Structural diversity, bioactivities, and biosynthesis of natural diterpenoid alkaloids. *Nat. Prod. Rep.* 37, 763–796. <https://doi.org/10.1039/d0np00002g>.
- Silva, M.A.E., Brand, A.L.M., Novaes, F.J.M., Rezende, C.M., 2022. Cafestol, kahweol and their acylated derivatives: antitumor potential, pharmacokinetics, and chemopreventive profile. *Food Rev. Int.* <https://doi.org/10.1080/87559129.2022.2141776>.
- Silva, M.L., Oliveira, C.S., dos Santos, W.J.O., Oliveira, V.X., Antar, G.M., Lago, J.H.G., Cerchiaro, G., 2022. Selective cytotoxicity of ent-kaurene diterpenoids isolated from *Baccharis lateralis* and *Baccharis retusa* (Asteraceae). *Arch. Pharm.* 355 <https://doi.org/10.1002/ardp.202200083>.
- Singh, N., Baby, D., Rajguru, J., Patil, P., Thakkannavar, S., Pujari, V., 2019. Inflammation and cancer. *Ann. Afr. Med.* 18 https://doi.org/10.4103/aam.aam_56_18.
- Sitarek, P., Kowalczyk, T., Synowiec, E., Merez-Sadowska, A., Bangay, G., Princiotto, S., Śliwiński, T., Rijo, P., 2022a. An evaluation of the novel biological properties of diterpenes isolated from *Plectranthus ornatus* codd. in vitro and in silico. *Cells* 11. <https://doi.org/10.3390/cells11203243>.
- Sitarek, P., Synowiec, E., Kowalczyk, T., Bangay, G., Śliwiński, T., Picot, L., Princiotto, S., Rijo, P., 2022b. Anticancer properties of *Plectranthus ornatus*-derived phytochemicals inducing apoptosis via mitochondrial pathway. *Int. J. Mol. Sci.* 23 <https://doi.org/10.3390/ijms231911653>.
- Sitarek, P., Synowiec, E., Kowalczyk, T., Bangay, G., Śliwiński, T., Picot, L., Princiotto, S., Rijo, P., 2022c. Anticancer properties of *Plectranthus ornatus*-derived phytochemicals inducing apoptosis via mitochondrial pathway. *Int. J. Mol. Sci.* 23 <https://doi.org/10.3390/ijms231911653>.
- Soejarto, D.D., Fong, H.H.S., Tan, G.T., Zhang, H.J., Ma, C.Y., Franzblau, S.G., Gyllenhaal, C., Riley, M.C., Kadushin, M.R., Pezzuto, J.M., Xuan, L.T., Hiep, N.T., Hung, N.V., Vu, B.M., Loc, P.K., Dac, L.X., Binh, L.T., Chien, N.Q., Hai, N.V., Bich, T.Q., Cuong, N.M., Southavong, B., Sydara, K., Bouamanivong, S., Ly, H.M., Van Thuy, T., Rose, W.C., Dietzman, G.R., 2005. Ethnobotany/ethnopharmacology and mass bioprospecting: issues on intellectual property and benefit-sharing. *J. Ethnopharmacol.* <https://doi.org/10.1016/j.jep.2005.05.031>.
- Son, N.T., 2019. Genus *Erythrophleum*: botanical description, traditional use, phytochemistry and pharmacology. *Phytochem. Rev.* <https://doi.org/10.1007/s11101-019-09640-0>.
- Sosef, M.S.M., Dauby, G., Blach-Overgaard, A., van der Burg, X., Catarino, L., Damen, T., Deblauwe, V., Dessein, S., Dransfield, J., Droissart, V., Duarte, M.C., Engledow, H., Fadeur, G., Figueira, R., Gereau, R.E., Hardy, O.J., Harris, D.J., de Heij, J., Janssens, S., Klomberg, Y., Ley, A.C., Mackinder, B.A., Meerts, P., van de Poel, J.L., Sonké, B., Stévant, T., Stoffelen, P., Svenning, J.C., Sepulchre, P., Zaiss, R., Wieringa, J.J., Couvreur, T.L.P., 2017. Exploring the floristic diversity of tropical Africa. *BMC Biol.* 15 <https://doi.org/10.1186/s12915-017-0356-8>.
- Sridevi, V., Giridhar, P., Ravishanker, G., 2011. Evaluation of roasting and brewing effect on antinutritional diterpenes-cafestol and kahweol in coffee. *Glob. J. Med. Res.* 11.
- Stévant, T., Dauby, G., Lowry, P., Blach-Overgaard, A., Droissart, V., Harris, D.J., Mackinder, A.B., Schatz, G.E., Sonké, B., Sosef, M.S.M., Svenning, J.C., Wieringa, J., Couvreur, T.L.P., 2019. A third of the tropical African flora is potentially threatened with extinction. *Sci. Adv.* 5 <https://doi.org/10.1126/sciadv.aax9444>.
- Su, K., Wang, C.F., Zhang, Y., Cai, Y.J., Zhang, Y.Y., Zhao, Q., 2016. The inhibitory effects of carnosic acid on cervical cancer cells growth by promoting apoptosis via ROS-regulated signaling pathway. *Biomed. Pharmacother.* 82 <https://doi.org/10.1016/j.biopha.2016.04.056>.
- Su, J.C., Cheng, W., Song, J.G., Zhong, Y.L., Huang, X.J., Jiang, R.W., Li, Y.L., Li, M.M., Ye, W.C., Wang, Y., 2019. Macrocyclic Diterpenoids from *Euphorbia helioscopia* and Their Potential Anti-inflammatory Activity. *J. Nat. Prod.* 82 <https://doi.org/10.1021/acs.jnatprod.9b00519>.
- Tae, N., Hung, T.M., Kim, O., Kim, N., Lee, S., Na, S., Min, B.S., Lee, J.H., 2017. A cassaine diterpene alkaloid, 3 β -acetyl-nor-erythrophamide, suppresses VEGF-induced angiogenesis and tumor growth via inhibiting eNOS activation. *Oncotarget* 8 (54), 92346–92358.
- Tang, B., Tang, F., Wang, Z., Qi, G., Liang, X., Li, B., Yuan, S., Liu, J., Yu, S., He, S., 2016. Upregulation of Akt/NF- κ B-regulated inflammation and Akt/Bad-related apoptosis signaling pathway involved in hepatic carcinoma process: suppression by carnosic acid nanoparticle. *Int. J. Nanomedicine* 11, 6401–6420. <https://doi.org/10.2147/IJN.S101285>.
- Tatipamula, V.B., Thonangi, C.V., Dakal, T.C., Vedula, G.S., Dhabhai, B., Polimati, H., Akula, A., Nguyen, H.T., 2022. Potential anti-hepatocellular carcinoma properties and mechanisms of action of clerodane diterpenes isolated from *Polyalthia longifolia* seeds. *Sci. Rep.* 12 <https://doi.org/10.1038/s41598-022-13383-y>.
- Teng, Y.N., Wang, Y., Hsu, P.L., Xin, G., Zhang, Y., Morris-Natschke, S.L., Goto, M., Lee, K.H., 2018. Mechanism of action of cytotoxic compounds from the seeds of *Euphorbia lathyris*. *Phytomedicine* 41. <https://doi.org/10.1016/j.phymed.2018.02.001>.
- Thawabteh, A.M., Thawabteh, A., Lelario, F., Bufo, S.A., Scrano, L., 2021. Classification, toxicity and bioactivity of natural diterpenoid alkaloids. *Molecules*. <https://doi.org/10.3390/molecules26134103>.
- The Atlantic Slave Trade, 2011. Choice Reviews Online 48. <https://doi.org/10.5860/choice.48-3412>.
- Thi Nguyen, T.T., To, D.C., Thi Vo, P.H., Tran, T.H., Nguyen, P.H., Nguyen, H.M., Tran, M.H., 2020. Cassaine diterpenoid amide from stem bark of *Erythrophleum fordii* suppresses cytotoxic and induces apoptosis of human leukemia cells. *Molecules* 25. <https://doi.org/10.3390/molecules25143304>.
- Thiyagarajan, V., Sivalingam, K.S., Viswanatha, V.P., Weng, C.F., 2016. 16-hydroxycleroda-3,13-dien-16,15-olide induced glioma cell autophagy via ROS generation and activation of p38 MAPK and ERK1/2. *Environ. Toxicol. Pharmacol.* 45 <https://doi.org/10.1016/j.etap.2016.06.005>.
- Tran, M.H., Nguyen, M.T.T., Nguyen, H.D., Nguyen, T.D., Phuong, T.T., 2015. Cytotoxic constituents from the seeds of Vietnamese *Caesalpinia sappan*. *Pharm. Biol.* 53 <https://doi.org/10.3109/13880209.2014.986686>.
- Tsai, Y.T., Sung, L.C., Haw, W.R., Chen, C.C., Huang, S.F., Liu, J.C., Cheng, T.H., Chen, P. Y., Loh, S.H., Tsai, C.S., 2018. Cafestol, a coffee diterpene, inhibits urotensin II-induced interleukin-8 expression in human umbilical vein endothelial cells. *Eur. J. Pharmacol.* 820 <https://doi.org/10.1016/j.ejphar.2017.12.030>.
- Tsai, J.Y., Rédei, D., Hohmann, J., Wu, C.C., 2020. 12-deoxyphorbol esters induce growth arrest and apoptosis in human lung cancer A549 cells via activation of PKC- δ /PKD/ERK signaling pathway. *Int. J. Mol. Sci.* 21 <https://doi.org/10.3390/ijms21207579>.
- van Wyk, B.E., Albrecht, C., 2008. A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Sutherlandia frutescens* (Fabaceae). *J. Ethnopharmacol.* <https://doi.org/10.1016/j.jep.2008.08.003>.
- Van Wyk, B.E., 2020. A family-level floristic inventory and analysis of medicinal plants used in Traditional African Medicine. *J. Ethnopharmacol.* <https://doi.org/10.1016/j.jep.2019.112351>.
- Vanti, G., Capizzi, M., Di Cesare Mannelli, L., Lucarini, E., Bergonzi, M.C., Ghelardini, C., Bilia, A.R., 2022. Escinosomes: safe and successful nanovesicles to deliver andrographolide by a subcutaneous route in a mice model of oxaliplatin-induced neuropathy. *Pharmaceutics* 14. <https://doi.org/10.3390/pharmaceutics14030493>.
- Vela, F., Ezzanad, A., Hunter, A.C., Macías-Sánchez, A.J., Hernández-Galán, R., 2022. Pharmacological potential of lathyrane-type diterpenoids from phytochemical sources. *Pharmaceutics* 15. <https://doi.org/10.3390/ph15070780>.
- Velmurugan, B.K., Wang, P.C., Weng, C.F., 2018. 16-hydroxycleroda-3,13-dien-15,16-olide and N-methyl-actinodaphine potentiate tamoxifen-induced cell death in breast cancer. *Molecules* 23. <https://doi.org/10.3390/molecules23081966>.
- Vergara, D., Simeone, P., Bettini, S., Tinelli, A., Valli, L., Storelli, C., Leo, S., Santino, A., Maffia, M., 2014. Antitumor activity of the dietary diterpene carnosol against a panel of human cancer cell lines. *Food Funct.* 5 <https://doi.org/10.1039/c4fo00023d>.
- Villareal, M.O., Sato, Y., Matsuyama, K., Isoda, H., 2018. Correction to: daphnane diterpenes inhibit the metastatic potential of B16F10 murine melanoma cells *in vitro* and *in vivo* (BMC Cancer (2018) 18 (856) DOI: 10.1186/s12885-018-4693-y). *BMC Cancer* 18, 1–11. <https://doi.org/10.1186/s12885-018-4805-8>.
- Wagner, H., Ulrich-Merzenich, G., 2009. Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine*. <https://doi.org/10.1016/j.phymed.2008.12.018>.
- Wang, Y.Y., He, Y., Yang, L.F., Peng, S.H., He, X.L., Wang, J.H., Lv, F., Hao, Y., Liu, M.Y., Yi, Z., Qiu, W.W., 2016. Synthesis of novel diterpenoid analogs with in-vivo antitumor activity. *Eur. J. Med. Chem.* 120, 13–25. <https://doi.org/10.1016/j.ejmech.2016.04.071>.
- Will, M., Claßen-Bockhoff, R., 2014. Why Africa matters: evolution of old world salvia (Lamiaceae) in Africa. *Ann. Bot.* 114 <https://doi.org/10.1093/aob/mcu081>.

- Williamson, E.M., 2001. Synergy and other interactions in phytomedicines. *Phytomedicine*. <https://doi.org/10.1078/0944-7113-00060>.
- Wu, T.H., Cheng, Y.Y., Chen, C.J., Ng, L.T., Chou, L.C., Huang, L.J., Chen, Y.H., Kuo, S.C., El-Shazly, M., Wu, Y.C., Chang, F.R., Liaw, C.C., 2014. Three new clerodane diterpenes from *polyalthia longifolia* Var. *Pendula*. *Molecules* 19. <https://doi.org/10.3390/molecules19022049>.
- Wu, W., Zhang, Y., Tang, S., Ye, M., Lu, J., Jiang, C., 2016. Anticancer potential of *Salvia miltiorrhiza* and its tanshinones: an efficacy perspective. *Botanics: Targets Therapy* 6, 45–58. <https://doi.org/10.2147/BTAT.S68097>.
- Wu, J., Guo, L., Qiu, X., Ren, Y., Li, F., Cui, W., Song, S., 2020. Genkwadaphnin inhibits growth and invasion in hepatocellular carcinoma by blocking DHCR24-mediated cholesterol biosynthesis and lipid rafts formation. *Br. J. Cancer* 123. <https://doi.org/10.1038/s41416-020-01085-z>.
- Wu, Y.J., Wei, W.C., Dai, G.F., Su, J.H., Tseng, Y.H., Tsai, T.C., 2020. Exploring the mechanism of flaccidoxide-13-Acetate in suppressing cell metastasis of hepatocellular carcinoma. *Mar. Drugs* 18. <https://doi.org/10.3390/md18060314>.
- Wu, W., Cao, Y., Cheng, L., Wang, L., Yu, Q., Peng, H., Zhou, F., Liu, H., Zhang, Q., 2022. Cryptotanshinone from *salvia miltiorrhiza* inhibits the growth of tumors and enhances the efficacy of chemotherapy in a gastric cancer mouse model. *Nat. Prod. Commun.* 17. <https://doi.org/10.1177/1934578x221130874>.
- Xia, Y., Lam, C.S., Li, W., Sarwar, M.S., Liu, K., Lee, K.M., Zhang, H.J., Tsang, S.W., 2019. Flexicaulin A, an ent-kaurane diterpenoid, activates p21 and inhibits the proliferation of colorectal carcinoma cells through a non-apoptotic mechanism. *Int. J. Mol. Sci.* 20. <https://doi.org/10.3390/ijms20081917>.
- Xing, H., An, L., Song, Z., Li, S., Wang, H., Wang, C., Zhang, J., Tuerhong, M., Abudukeremu, M., Li, D., Lee, D., Xu, J., Lall, N., Guo, Y., 2020. Anti-inflammatory ent-kaurane Diterpenoids from *Isodon serra*. *J. Nat. Prod.* 83. <https://doi.org/10.1021/acs.jnatprod.9b01281>.
- Xu, W.H., Liu, W.Y., Liang, Q., 2018. Chemical constituents from croton species and their biological activities. *Molecules*. <https://doi.org/10.3390/molecules23092333>.
- Xue, X.B., Lv, T.M., Hou, J.Y., Li, D.Q., Huang, X.X., Song, S.J., Yao, G.D., 2023. Vibsane-type diterpenoids from *Viburnum odoratissimum* inhibit hepatocellular carcinoma cells via the PI3K/AKT pathway. *Phytomedicine* 108. <https://doi.org/10.1016/j.phymed.2022.154499>.
- Yan, M., Li, G., Petiwala, S.M., Householter, E., Johnson, J.J., 2015. Standardized rosemary (*Rosmarinus officinalis*) extract induces Nrf2/sestrin-2 pathway in colon cancer cells. *J. Funct. Foods* 13. <https://doi.org/10.1016/j.jff.2014.12.038>.
- Yan, X., Zhang, L., Cao, Y., Yao, W., Tang, Y., Ding, A., 2016. An ingenol derived from *Euphorbia kansui* induces hepatocyte cytotoxicity by triggering G0/G1 cell cycle arrest and regulating the mitochondrial apoptosis pathway *in vitro*. *Molecules* 21. <https://doi.org/10.3390/molecules21060813>.
- Yang, H., Ping Dou, Q., 2010. Targeting apoptosis pathway with natural terpenoids: implications for treatment of breast and prostate cancer. *Curr. Drug Targets* 11, 733–744. <https://doi.org/10.2174/138945010791170842>.
- Yang, T., Wang, S., Li, H., Zhao, Q., Yan, S., Dong, M., Liu, D., Chen, X., Li, R., 2020. Lathyrane diterpenes from *Euphorbia lathyris* and the potential mechanism to reverse the multi-drug resistance in HepG2/ADR cells. *Biomed. Pharmacother.* 121. <https://doi.org/10.1016/j.biopha.2019.109663>.
- Yang, P., Jiang, P.W., Li, C., Gao, M.X., Sun, Y.S., Zhang, D.Y., Du, W.Q., Zhao, J., Shi, S. T., Li, Y., Yang, T., Cheng, L., Li, M.H., 2021. Cdc25C/cdc2/cyclin B, raf/MEK/ERK and PERK/eIF2α/CHOP pathways are involved in forskolin-induced growth inhibition of MM.1S cells by G2/M arrest and mitochondrion-dependent apoptosis. *Cell Cycle* 20, 2402–2412. <https://doi.org/10.1080/15384101.2021.1983280>.
- Yashaswini, S., Vasundhara, M., 2011. *Coleus (Plectranthus barbatus)* - a multipurpose medicinal herb. *Int. Res. J. Pharmacy* 2.
- Yerragunta, V., Waghray, K., Shivraj, Subhashini, N.J.P., 2021. Anti-cancer activity of andrographolide: a review. *J. Pharm. Res. Int.* <https://doi.org/10.9734/jpri/2021/v33i43b32519>.
- Yu, X.Q., Maki, M., Drew, B.T., Paton, A.J., Li, H.W., Zhao, J.L., Conran, J.G., Li, J., 2014. Phylogeny and historical biogeography of *Isodon* (Lamiaceae): rapid radiation in south-west China and Miocene overland dispersal into Africa. *Mol. Phylogenet. Evol.* 77. <https://doi.org/10.1016/j.ympev.2014.04.017>.
- Yu, C.C., Chen, C.A., Fu, S.L., Lin, H.Y., Lee, M.S., Chiou, W.Y., Su, Y.C., Hung, S.K., 2018. Andrographolide enhances the anti-metastatic effect of radiation in Ras-transformed cells via suppression of ERK-mediated MMP-2 activity. *PLoS ONE* 13. <https://doi.org/10.1371/journal.pone.0205666>.
- Yuan, X.L., Mao, X.X., Du, Y.M., Yan, P.Z., Hou, X.D., Zhang, Z.F., 2019. Anti-tumor activity of cembranoid-type diterpenes isolated from *Nicotiana tabacum* L. *BioMolecules* 9. <https://doi.org/10.3390/biom9020045>.
- Yue, G.G.L., Liang, X.X., Li, X.L., Lee, J.K.M., Gao, S., Kwok, H.F., Lau, C.B.S., Xiao, W.L., 2020. Immunomodulatory and antitumor bioactive labdane diterpenoids from *Leonurus japonicus*. *J. Pharmacy Pharmacol.* 72, 1657–1665. <https://doi.org/10.1111/jphp.13348>.
- Zeng, B., Wei, A., Zhou, Q., Yuan, M., Lei, K., Liu, Y., Song, J., Guo, L., Ye, Q., 2022. Andrographolide: a review of its pharmacology, pharmacokinetics, toxicity and clinical trials and pharmaceutical researches. *Phytother. Res.* 36, 336–364. <https://doi.org/10.1002/ptr.7324>.
- Zhang, S., Feng, N., Huang, J., Wang, M., Zhang, L., Yu, J., Dai, X., Cao, J., Huang, G., 2020. Incorporation of amino moiety to alepterolic acid improve activity against cancer cell lines: synthesis and biological evaluation. *Bioorg. Chem.* 98. <https://doi.org/10.1016/j.bioorg.2020.103756>.
- Zhang, Y.Y., Chen, J.J., Li, D.Q., Zhang, Y., Wang, X.B., Yao, G.D., Song, S.J., 2021. Network pharmacology uncovers anti-cancer activity of vibsane-type diterpenes from *Viburnum odoratissimum*. *Nat. Prod. Res.* 35. <https://doi.org/10.1080/14786419.2019.1582047>.
- Zhang, J., Li, C., Zhang, L., Heng, Y., Wang, S., Pan, Y., Cai, L., Zhang, Y., Xu, T., Chen, X., Hoffman, R.M., Jia, L., 2022. Andrographolide, a diterpene lactone from the Traditional Chinese Medicine *Andrographis paniculate*, induces senescence in human lung adenocarcinoma via p53/p21 and Skp2/p27. *Phytomedicine* 98. <https://doi.org/10.1016/j.phymed.2022.153933>.
- Zhao, H., Zhang, X., 2021. Sugirol suppresses the growth, migration, and invasion of human endometrial cancer cells via induction of apoptosis and autophagy. *3 Biotech* 11. <https://doi.org/10.1007/s13205-020-02625-3>.
- Zheng, J.H., Lin, S.R., Tseng, F.J., Tsai, M.J., Lue, S.I., Chia, Y.C., Woon, M., Fu, Y.S., Weng, C.F., 2019. Clerodane diterpene ameliorates inflammatory bowel disease and potentiates cell apoptosis of colorectal cancer. *BioMolecules* 9. <https://doi.org/10.3390/biom9120762>.
- Zhu, J., Wang, R., Lou, L., Li, W., Tang, G., Bu, X., Yin, S., 2016. Jatrophone diterpenoids as modulators of P-glycoprotein-dependent multidrug resistance (MDR): advances of structure-activity relationships and discovery of promising MDR reversal agents. *J. Med. Chem.* 59, 6353–6369. <https://doi.org/10.1021/acs.jmedchem.6b00605>.
- Zhu, Q.F., Qi, Y.Y., Zhang, Z.J., Fan, M., Bi, R., Su, J., Wu, X.De, Shao, L.D., Zhao, Q.S., 2018. Vibsane-type diterpenoids from *viburnum odoratissimum* and their cytotoxic and HSP90 inhibitory activities. *Chem. Biodivers.* 15. <https://doi.org/10.1002/cbdv.201800049>.
- Zofou, D., Ntie-Kang, F., Sippl, W., Efang, S.M.N., 2013. Bioactive natural products derived from the Central African flora against neglected tropical diseases and HIV. *Nat. Prod. Rep.* <https://doi.org/10.1039/c3np70030e>.