Anticancer attributes of desert plants: a review

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The ever-increasing emergence of the resistance of mammalian tumor cells to chemotherapy and its severe side effects reduces the clinical efficacy of a large variety of anticancer agents that are currently in use. Thus, despite the significant progress in cancer therapeutics in the last decades, the need to discover and to develop new, alternative, or synergistic anticancer agents remains. Cancer prevention or chemotherapy based on bioactive fractions or pure components derived from desert plants with known cancer-inhibiting properties suggests promising alternatives to current cancer therapy. Plants growing on low nutrient soils and/or under harsh climatic conditions, such as extreme temperatures, intense solar radiation, and water scarcity, are particularly susceptible to attack from reactive oxygen species and have evolved efficient antioxidation defense systems. The many examples of desert plants displaying anticancer effects as presented here indicates that the same defensive secondary metabolites protecting them against the harsh environment may also play a protective or a curative role against cancer, as they also do against diabetes, neurodegenerative, and other acute and chronic diseases. The present review highlights a plethora of studies focused on the antineoplastic properties of desert plants and their prinicipal phytochemicals, such as saponins, flavonoids, tannins, and terpenes. Although many desert plants have been investigated for their antitumor properties, there are many that still remain to be explored – a challenge for the prospective cancer therapy of the future. ***Anti-Cancer Drugs*** **23:255–271** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The unique natural defense systems of plants growing under harsh desert stress conditions depend on certain defensive secondary metabolites. These compounds evolve largely to deter pathogens and herbivores, such as insects and mammals, whereas their levels in the plant's tissues are believed to be both environmentally induced and genetically controlled. Plants growing on low nutrient soils and/or under harsh climatic conditions, such as extreme temperatures, intense solar radiation, and water scarcity, are often more dependent on evolved chemical defenses than their counterparts growing under milder conditions. Such plants are under constant attack by reactive oxygen species (ROS) and have evolved efficient antioxidation defense systems, including antioxidative enzymes or nonenzymatic antioxidants. The high concentrations of defensive metabolites in desert plants impart antioxidant as well as antifungal, antibacterial, antiviral, anthelmintic, and antimutagenic capabilities to the plant. Extraordinary nonenzymatic antioxidative capacity might be a characteristic of plants living in extremely stressful environments [1]. ROS have been shown to be involved in the pathogenesis of infections, in cardiovascular and neurodegenerative diseases, and the early stages of carcinogenesis [2–4].

Much of the research on desert plants has focused on their often-occurring essential oils. The chemical profiles of many of these oils have been established, and their antioxidant, antibacterial, and insecticidal activities have been enumerated [5–7]. Essential oils are assumed to provide resistance against drought. For example, the concentration of the essential oil of *Artemisia tridentata*, a desert plant growing in western US, was found to be 0.04% in May, 0.23% in June, 0.39% in July, and 0.83% in September, suggesting that these variations reflect a drought resistance developed by the plant [8]. However, essential oils comprise usually less than 1% of dried plant material and neither manifest the entire plant's capability to cope with the environment nor the plant's entire phytochemical reservoir of valuable components.

Antibacterial, antifungal, antioxidative, and antidiabetic properties of desert plants were found in aqueous extracts of their aerial parts. Aqueous extracts of desert plants were studied against fish bacterial pathogenes, showing inhibition of *Aeromonas hydrophila*, *Photobacterium damselae*, *Streptococcus iniae*, and *Vibrio alginolyticus* [9], whereas ethyl acetate extracts of the aerial parts of *Varthemia iphionoides* showed pronounced antibacterial activity [10]. Antifungal flavonoids were also extracted from the aerial and

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subterranean parts of *V. iphionoides*, using a multistage extraction technique, followed by chromatographic separations, and showing antifungal activity against *Fusarium solani*, *Candida tropicalis*, and *Aspergilus parasiticus* [11]. Many desert plants also possess antioxidant and antidiabetic properties [12–17].

The aim of this article is to review the work performed to date on desert plants in cancer research. To the best of our knowledge, such an attempt is a first of its kind.

Cancer inhibitory attributes of phenolic secondary metabolites

The overproduction of ROS has been considered to cause several diseases, such as liver cirrhosis, atherosclerosis, diabetes, cancer, and neurodegenerative diseases. Therefore, compounds that can scavenge reactive free radicals have great potential in ameliorating these disease processes. Antioxidants – compounds capable of scavenging ROS – thus play an important role in protecting the human body against the damage they cause [18].

The antioxidative properties of phenolic compounds (e.g. phenolic acids, flavonoids, quinones, and tannins) have been well established. Polyphenols are natural antioxidants assumed to function as terminators of free radical chains or as chelators of redox-active metal ions capable of catalyzing lipid peroxidation [19]. A positive linear correlation between antioxidative chemical activity (the capability to scavenge oxygen free radicals) and total phenolic content in plants was found [16]. Also, the molecular structure of flavonoids correlates with their radical-scavenging activity [20], but the in-vivo antioxidant efficacy of flavonoids has been less thoroughly documented [21].

Saponins as cancer inhibitors

Triterpenoid and steroidal glycosides, collectively referred to as saponins, are bioactive compounds present naturally in many plants. Saponins are a major family of secondary metabolites containing a sugar moiety glycosidically linked to a hydrophobic aglycone (sapogenin). In recent years, interest in saponins has emerged due to increased knowledge of their diverse properties as natural detergents and foaming agents, cardiac, immunostimulating, and anticancer activity, and other health-promoting functions [22,23].

Saponins, like flavonoids, tannins, and terpenes, are defensive secondary metabolites that allow plants to cope with the environmental conditions (storing and conserving water, resisting predators, and surviving severe weather conditions). Saponins have detergent and surfactant properties because they contain both water-soluble (the sugar moiety) and fat-soluble (sapogenin) subunits. The sapogenin fat-soluble nucleus, that is, choline, steroid, or triterpenoid, is attached by C3 or an ether bond, to a water-soluble side-chain carbohydrate. As a consequence of their surface active properties, saponins form stable foams. Plant sources of saponins include yucca, christmas rose (*Helleborus niger*), horse chestnuts (*Aesculus hipppcastanum*), asparagus fern (*Asparagus officinalis*), daisies (*Bellis perennis*), chickpeas, soybeans, alfalfa, and others [24].

The cholesterol-binding property of saponins relates to their ability to inhibit the growth of, or kill, cancer cells, while leaving normal cells unaffected. That cancer cells have more cholesterol-type compounds in their membranes than normal cells and that saponins binding membrane cholesterol interfere with cell growth and division provide clues toward understanding the anticancer selectivity of saponins [25].

Binding of bile acids by saponins has important implications. Bile acids excreted in the bile (primary bile acids) are metabolized by bacteria in the colon, producing secondary bile acids, which may promote colon cancer. By binding to primary bile acids, saponins reduce the formation of the secondary bile acids and, concomitantly, the risk of colon cancer. Feeding saponins to laboratory animals reduced the number of preneoplastic colon lesions in mice and also dose-dependently inhibited the growth of human carcinoma cells in culture [26]. The proposed mechanisms of anticarcinogenic properties of saponins include antioxidant effects, direct and indirect cytotoxicity to cancer cells, immune modulation, acid and neutral sterol metabolic modulation, and regulation of cell proliferation. The polarity, hydrophobicity, and nature of the reactive groups of saponins are important determinants of their biological properties. For example, structure–activity relations indicated that the bioactivity of soyasaponins increased with increasing lipophilicity [25].

Recent studies have indicated that dietary sources of saponins offer a preferential chemopreventive strategy in lowering the risk of human cancers. For example, soybean saponins suppressed the growth of HT-29 colon cancer cells. The most potent compounds were the aglycones soyasapogenol A and B, inducing almost complete suppression of cell growth. In-vitro fermentation tests suggested that colonic microflora readily hydrolyze the soyasaponins to their bioactive aglycones [24]. Soybean extracts also exhibited synergistic antiproliferative activity against an ovarian tumor cell line (OVCA 433), with an IC_{50} of 1.1 μmol/l [27].

The glycosides naringin, rutin, and baicalin in soybean extracts also exert anticancer actions. Naringin has been reported to exhibit anticarcinogenic properties [28]. In humans, rutin attaches to the iron ion (Fe^{2+}), preventing it from binding to hydrogen peroxide, which would otherwise create highly reactive free radicals that may damage cells [29]. Baicalin has a cytotoxic effect on leukemia-derived T cells [30]. Soybean saponin (soyasaponin I) exhibits estrogenic activities through its binding to human

estrogen receptors, acting as estrogen antagonists, and the aglycone sapogenol shows antiproliferative activity against MCF-7 cells [31].

Saponins in desert plants

Many desert plants contain substantial amounts of steroid and triterpene saponins. The basic mechanisms by which some xerophytes (cacti, yucca, and agaves, mesquite and ironwood trees, ocotillo, and greasewood and creosote bushes) store and conserve water, resist predators, and survive severe weather conditions are likely due, at least in part, to saponins present in them. For example, the structural matrix of the agave (century plant) contains, in addition to the usual polyuronides, substantial amounts of steroid and triterpene saponins. In the aloes, the solid interior is a mucilaginous polyuronide matrix containing ~99.2% water [32].

Saponins in certain desert plants are considered responsible for their medicinal attributes. One of the most known plants is yucca (*Yucca schidigera*), a xerophyte belonging to the Agavaceae family, growing in the arid Mexican desert country of Baja California [33,34]. Another desert plant is Quillaja (*Quillaja saponaria*), a Quillajaceae family drought-resistant evergreen tree native to warm-temperate central Chile and used in folk medicine by the Andean people [33,35].

Antitumor effects of saponins present in desert plants

Table 1 presents several desert plants in alphabetical order and provides information on their habitats and anticancer actions. Table 2 presents the structures of components identified in the plants to exhibit anticancerous properties. Below, we elaborate on some of the highlights of this research and the plants studied.

Balanites aegyptiaca is a tree native to much of Africa and parts of the Middle East and is of great medicinal interest due to its cytotoxic and cytostatic compounds. The antiproliferative activity and mode of action of spirostane (SAP-1016 and SAP-884) and furostane (KE-1046 and KE-1064) saponins isolated from *B. aegyptiaca* were investigated. The compounds SAP-1016 (3β-*O*-β-D-xylopyranosyl-(1-3)-β-D-glucopyranosyl-(1-4)-[α-L-rhamnopyranosyl-(1-2)]-β-D-glucopyranoside) exhibited potent antiproliferative activity against MCF-7 human breast cancer cells and HT-29 human colon cancer cells, with IC_{50} values of 2.4 ± 0.35 and 3.3 ± 0.19 μmol/l, respectively, compared with dioscin, one of the most potent cytotoxic spirostane saponins, with IC_{50} values of 3.1 ± 0.39 and 4.9 ± 0.32 μmol/l, respectively. Significant antiproliferative activity of SAP-1016 was also observed compared with a well-known anticancer agent, cisplatin, against both MCF-7 human breast cancer cells and HT-29 human colon cancer cells. Additional significant selectivity of growth inhibition between MCF-7 breast cancer cells and HFF normal cells was detected with the furostane saponins. Treatments of HT-29 cells with 5 μmol/l SAP-1016 for 24 h generated caspase-3 cleavage and therefore apoptosis activation [45].

Four saponins isolated from the seeds of *Balanites aegyptica* exhibited cytostatic activity against P-388 lymphocytic leukemia-cultured cells [46]. A mixture of the steroidal saponins balanitin-6 and balanitin-7 (Bal 6/7), isolated from *B. aegyptiaca* kernels, demonstrated appreciable anticancer effects in human cancer cell lines *in vitro*. Bal 6/7 displayed higher antiproliferative activity than etoposide and oxaliplatin, although the mixture was appreciably less active than SN38 and markedly less active than taxol. Bal 6/7 demonstrated the highest activity against A549 non-small-cell lung cancer (IC_{50} = 0.3 μmol/l) and U373 glioblastoma (IC_{50} = 0.5 μmol/l) cell lines. It was found that Bal 6/7 is more a cytotoxic compound than a cytostatic one, but Bal 6/7 does not appear to mediate its antiproliferative effects by inducing apoptotic cell death. Computer-assisted cellular imaging has revealed that Bal 6/7 does not induce detergent-like effects in A549 non-small-cell lung cancer and U373 glioblastoma, unlike certain saponins. Furthermore, there is an indication that its in-vitro anticancer activities result at least partly from the depletion of $[ATP]_i$, leading, in turn, to major disorganization of actin cytoskeleton, ultimately resulting in the impairment of cancer cell proliferation and migration. In contrast to a number of natural products acting as anticancer agents, Bal 6/7 does not induce an increase in intracellular ROS. *In vivo*, Bal 6/7 increased the survival time of mice bearing murine L1210 leukemia grafts to the same extent as that reported for vincristine. These preliminary in-vivo data suggest that novel semisynthetic derivatives of balanitin-6 and balanitin-7 could be generated with potentially improved in-vitro and in-vivo anticancer activity and a reduced in-vivo toxicity, thus markedly improving the therapeutic ratio [47].

Extracts derived from *Agave schottii*, a Sonora Desert xerophyte plant of the Agavaceae family, were effective inhibitors of a Walker carcinoma 256 tumor system. The active material was shown to be a saponin [37].

The Mojave yucca (*Yucca schidigera*) is a flowering plant of the Mojave Desert and Sonoran Desert of southeastern California, Baja California, southern Nevada, and western Arizona. This plant contains steroid saponins. A Japanese patent claims that extracts derived from the stem or the root of *Y. schidigera* display carcinostatic and mutagenesis-inhibitory effects, and are thus capable of inhibiting tumors [78].

A recently patented anticancer preparation claims to contain desert plant extracts. The plants were selected from Schisandra (such as *Schizandra chinensis*), Trichosanthes (such as *Trichosanthes kirilowii* Maxim), Glycine

Table 1 Anticancer activities of desert plants and desert plant-derived constituents

Name of plant	Desert	Part studied	Active compounds	Anticancer effects	References
Acacia victoriae	Western and central Australia	Seed pods	Saponins, avicin D, and avicin G	Exhibits cytotoxicity in human T cell leukemia cells	Jayatilake *et al.* [36]
Agave schottii	Sonoran	Not specified	Saponin and gitogenin	Inhibits Walker carcinoma 256	Bianchi and Cole [37]
Ambrosia ambrosoide	Sonoran	Rhizosphere fungi	Terrequinone A and terre-furanose	Inhibits the growth of NCI-H460, MCF-7, SF-268, and MIA PaCa-2 cells	He *et al.* [38]
Ammopiptanthus mongolicus (Leguminosae)	Northwest Gobi	Aerial parts	Not specified	Inhibits liver cancer	Jia [39]
Anemopsis californica	Southwest US, North Mexico	Roots	Thymol, piperitone, and methyleugenol	Inhibits the growth of AN3CA and HeLa cell lines	Medina-Holguín *et al.* [40]
Argania spinosa	Southwest Morocco	Seed oil	Linoleic, oleic acids, tocopherols, polyphenols, sterols, carotenoids, xanthophylls, and squalene	Inhbits the proliferation of DU145, LNCaP, and PC-3 prostate cancer cells	Drissi *et al.* [41]; Bennani *et al.* [42]
Artemisia campestris	South Tunisia	Aerial parts	Not specified	Exhibits growth inhibition of HT-29 human colon cancer cells	Akrout *et al.* [43]
Artemisia monosperma	Mediterranean woodlands and shrublands, deserts and extreme deserts	Not specified	Capillin	Inhibits the proliferation of HT29 colon carcinoma, MIA PaCa-2 pancreatic carcinoma, HEp-2 larynx carcinoma, and A549 lung carcinoma cells	Whelan and Ryan [44]
Balanites aegyptiaca	Africa, Levant	Seed and root	Saponins, spirostane, and furostane	Shows antiproliferative effects in MCF-7 breast cancer and HT-29 colon cancer cells	Beit-Yannai *et al.* [45]
			Balanitin-6 and balanitin-7	Induces cytotoxicity in P-388 lymphocytic leukemia, A549 non-small-cell-lung cancer and U373 glioblastoma cells	Pettit *et al.* [46]
			Balanitin-6 and balanitin-7	Improves the survival of mice bearing murine L1210 leukemia xenografts	Gnoula *et al.* [47]
Calotropis procera (Asclepiadaceae)	Caribbean, Central America, South America, Africa, India, and Israel	Aerial parts	Laticifer proteins	Inhibits the growth of sarcoma 180 in mice	Oliveira *et al.* [48]
		Roots	Not specified	Suppreses the proliferation of HepG2 cells through apoptotic and cell cycle disruptive mechanisms	Mathur *et al.* [49]
		Leaves	Cardiotonic steroid	Shows antiproliferative and cell death-inducing activities *in vitro*	Juncker *et al.* [50]
		Stems	Not specified	Displays antitumor cytotoxic effects against cancer cells; inhibits the growth of sarcoma 180 tumor	Magalhaes *et al.* [51]
Calligonum comosum (Polygonaceae)	Middle-eastern and Asian desert sands	Rhizosphere fungi and aerial parts	Dehydrodicatechin A	Inhibits the growth of Ehrlich ascites cells	Badria *et al.* [52]
Centaurea eryngioides (Compositae)	Israeli Negev	Aerial parts	Lupeol acetate, lupeol, saturated hydrocarbon, sitosterols, β-sitosterol glucoside, negletein, negletein-6-glucoside, pinocembrin, and pinocembrin-5,7-diglycoside	Exerts antitumor activities	Sarg *et al.* [53]
Commiphora opobalsamum	Levant	Resinous exudates	Sesquiterpenoids, 1(10)*E*,2*R*,4*R*)-2-methoxy-8,12-epoxygermacra-1(10),7,11-trien-6-one, 2-methoxy-5-acetoxy-furanogermacr-1(10)-en-6-one	Inhibits the proliferation of hormone-dependent prostate cancer cells	Kong *et al.* [54]; Shen *et al.* [55]
Ephedra fasciculata	Sonoran	Endophyte fungus	Radicicol	Inhibits the chaperon HSP90	Wang *et al.* [56]
Hammada scoparia	North Africa, southwest Asia	Stem and leaves	Rutin	Exhibits cytotoxicity against acute myeloid leukemia cells; suppresses tumor metastasis	Author not specified [57]

Table 1 (*continued*)

Name of plant	Desert	Part studied	Active compounds	Anticancer effects	References
Larrea divaricata Cav. or *Corillea tridentate*	US–Mexico border	Leaves	Nordihydroguaiaretic acid and terameprocol	Possesses antitumor activities	Chen [58]
Peganum harmala(Harmal)	East Mediterranean, Levant	Seeds	Harmine	Exhibits antitumor and antiangiogenic effects in xenografted B16F-10 tumor in mice	Hamsa and Kuttan [59]
			Harmaline	Abrogates lymphoma and gastrointestinal tumors	Wang [60]
			Harmine and harmaline	Shows growth-inhibitory properties in melanoma, renal, and breast cancer cells	Berrougui *et al.* [61]
Pituranthos tortuosus	Levant	Stems, leaves, and aerial parts	Not specified	Displays antiproliferative and proapoptotic effects in L1210 and K562 leukemia cell lines	Abdelwahed *et al.* [62]
			Terpinen-4-ol, sabinene, γ-terpinene, and β-myrcene	Inhibits the growth of HepG2, HCT116, and MCF-7 cells	Abdallah and Ezzat [63]
Pulicaria crispa (Forssk.) Oliv.	Israel, Levant	Aerial parts	Guaianolide sesquiterpenes and 5,10-epi-2,3-dihydroaromatin	Shows cytotoxicity in EJ-38 human bladder carcinoma cell line	Stavri *et al.* [64]
			Sesquiterpene lactones and axillarin	Exhibits anticancer cytoxic effects	Al-Yahya *et al.* [65]
Quillaja saponaria (Molina)	South America	Bark	Furostanol saponins	Inhibits the growth of KB human oral epidermoid carcinoma cells	Akhov *et al.* [66]
			Saponin fraction	Induces apoptosis in U937B lymphoma cells	Hu *et al.* [67]
			Quillaja saponaria-21 fraction	Modulates antibody and T-cell responses to anticancer vaccines	Ragupathi *et al.* [68]
				Exhibits immunomodulatory effects in melanoma *in vivo*	Ragupathi *et al.* [69]
			Saponins	Stimulates immune response and production of cytotoxic T-lymphocytes	Sun *et al.* [70]
Retama raetam (Papilionaceae)	East Mediterranean	Leaves and seeds	Not specified	Exerts cytotoxicity in COR-L23 large cell lung carcinoma cells	Conforti *et al.* [71]
Salvadora persica (Salvadoraceae)	Sudan	Leaves, stems	Not specified	Exhibits cytotoxic effects in KB, Saos-2, J744 A1, and gingival fibroblast cells	Rajabalian *et al.* [72]
Teucrium polium	Levant, south Europe	Aerial parts	Not specified	Inhibits the proliferation, invasion, and motility of PC-3 and DU-145 prostate cancer cells	Kandouz *et al.* [73]
				Augments the cytotoxic and apoptotic activities of anticancer drugs	Rajabalian [74]
Thymelaea hirsuta	South Tunisia and Israel	Aerial parts	Not specified	Shows antitumor growth inhibition of HT-29 human colon cancer cells	Akrout *et al.* [43]
		Roots	Daphnoretin	Exhibits cytotoxicity in prolifearing mammalian cells	Abou-Karam *et al.* [75]
Valeriana officinalis	Sonoran	Roots and rhizomes	Iridoids	Inhibits cell migration	Xu *et al.* [76]
Varthemia iphionoides	Middle-eastern desert and semidesert zones	Aerial parts	Saponins and 3-oxocostusic acid	Retards the proliferation of HL-60 human lymphocytic leukemia cells	Al-Dabbas *et al.* [77]
Yucca schidigera	Mojave and Sonoran	Stem and roots	Steroid saponin	Displayed carcinostatic and mutagenesis-inhibitory effects	Kaminobe *et al.* [78]
			Not specified	Induces apoptosis and cell cycle arrest; inhibits angiogenesis	Peng *et al.* [79]
			Furostanol saponins	Inhibits the growth of KB human oral epidermoid carcinoma cells	Akhov *et al.* [66]

[such as *Glycine max* (L.) Merr.], and yucca (such as *Y. schidigera*). The product was claimed to induce apoptosis or cell cycle stasis and inhibit angiogenesis or tumor cell metastasis, and to be useful for the treatment of cancer and cell proliferation disorders [79].

The influence of furostanol saponins from *Q. saponaria* and *Y. schidigera* was investigated on human oral cavity epidermoid carcinoma cells of the KB line. Furostanol saponins of these plants at a concentration of 25–50 μg/ml inhibited the growth of these cells by 69–73% [66].

Table 2 Structures of anticancer compounds derived from various desert plants

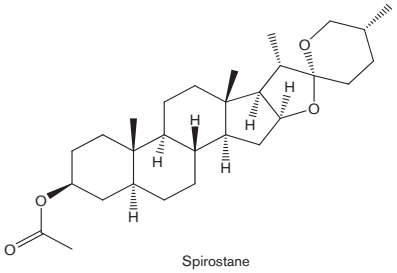
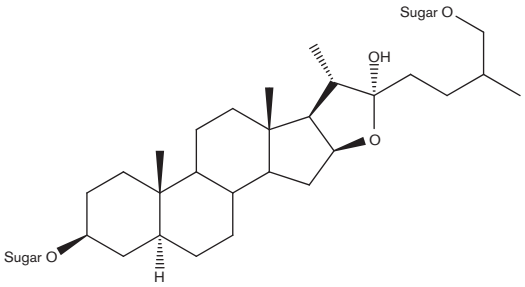
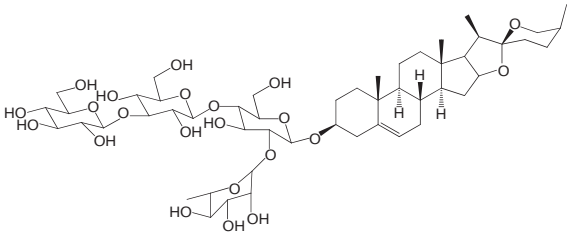
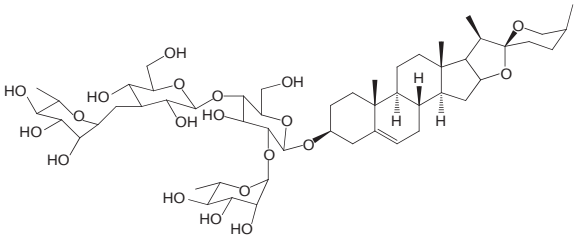
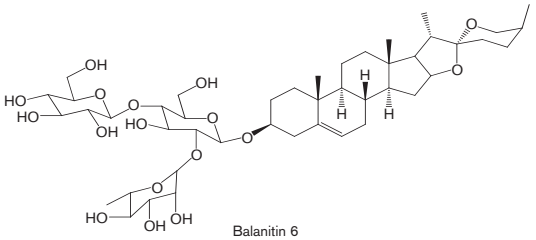
Compound	Chemical class	Plant source	References
 Spirostane	Steroidal saponin	*Balanites aegyptiaca*	Beit-Yannai *et al.* [45]
 Furostane	Steroidal saponin	*B. aegyptiaca*	Beit-Yannai *et al.* [45]
 Balanitin 4	Steroidal saponin	*B. aegyptiaca*	Pettit *et al.* [46]
 Balanitin 5	Steroidal saponin	*B. aegyptiaca*	Pettit *et al.* [46]
 Balanitin 6	Diosgenyl saponin	*B. aegyptica*	Pettit *et al.* [46]; Gnoula *et al.* [47]

Table 2 (*continued*)

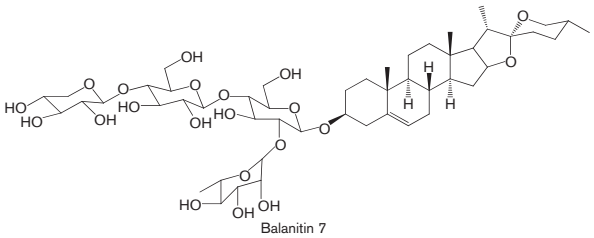
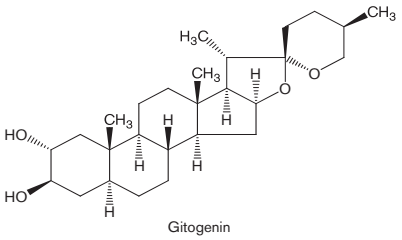
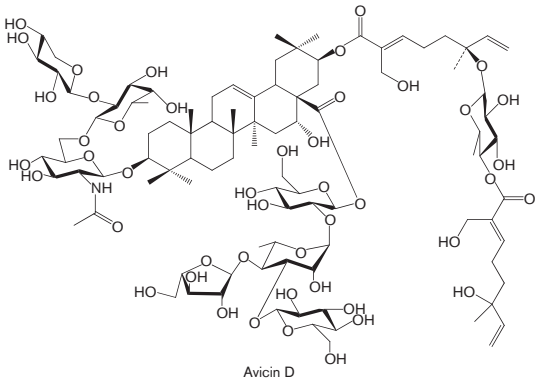
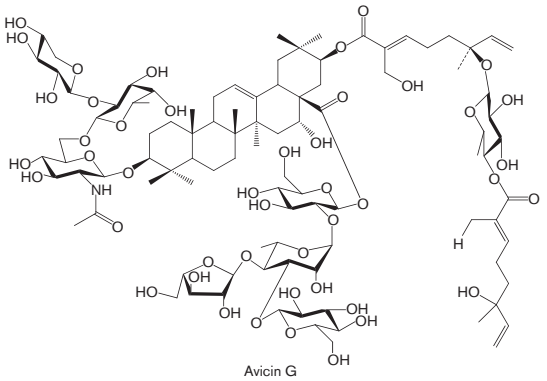
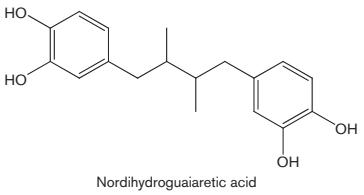
Compound	Chemical class	Plant source	References
 Balanitin 7	Diosgenyl saponin	*B. aegyptica*	Pettit *et al.* [46]; Gnoula *et al.* [47]
 Gitogenin	Steroidal saponin	*Agave schottii*	Bianchi and Cole [37]
 Avicin D	Triterpenoid	*Acacia victoriae*	Jayatilake *et al.* [36]
 Avicin G	Triterpenoid	*A. victoriae*	Jayatilake *et al.* [36]
 Nordihydroguaiaretic acid	Phenol carboxylic acid	*Larrea divaricata* Cav.	Chen *et al.* [58]

Table 2 (*continued*)

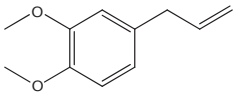
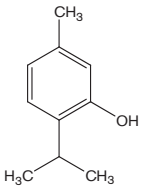
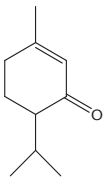
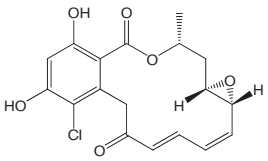
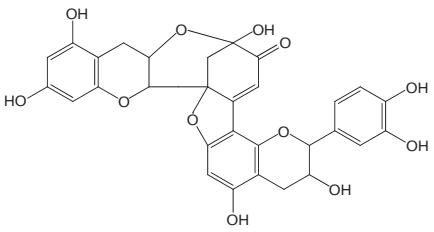
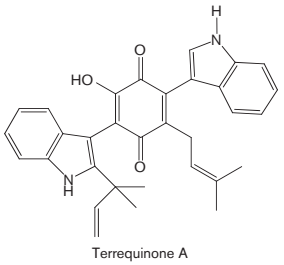
Compound	Chemical class	Plant source	References
 Methyl eugenol	Phenylpropanoid	*Anemopsis californica*	Medina-Holguín *et al.* [40]
 Thymol	Monoterpene phenol	*A. californica*	Medina-Holguín *et al.* [40]
 Piperitone	Monoterpene ketone	*A. californica*	Medina-Holguín *et al.* [40]
 Radicicol	Macrolactone	*Ephedra fasciculata*	Turbyville *et al.* [80]; Wang *et al.* [56]
 Dehydrodicatechin A	Flavonoid	*Calligonum comosum*	Badria *et al.* [52]
 Terrequinone A	Bisindolyl benzoquinone	*Ambrosia ambrosoide*	He *et al.* [38]

Table 2 (*continued*)

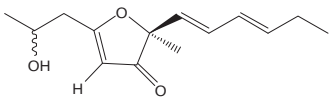
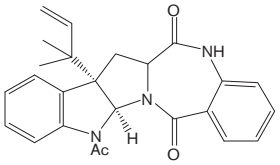
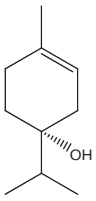
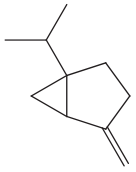
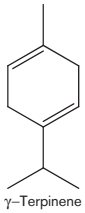
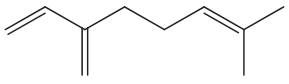
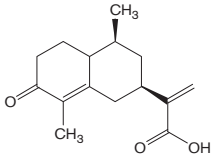
Compound	Chemical class	Plant source	References
 Terrefuranone	Furanone	*A. ambrosoide*	He *et al.* [38]
 *N*-acetyl aszonalemin (LL-S490β)	Aszonalemin	*A. ambrosoide*	He *et al.* [38]
 Terpinen-4-ol	Monoterpene	*Pituranthos tortuosus*	Abdallah and Ezzat [63]
 Sabinene	Bicyclic monoterpene	*P. tortuosus*	Abdallah and Ezzat [63]
 γ–Terpinene	Monoterpene	*P. tortuosus*	Abdallah and Ezzat [63]
 β-Myrcene	Monoterpene	*P. tortuosus*	Abdallah and Ezzat [63]
 3-Oxocostusic acid	Sesquiterpene	*Varthemia iphionoides*	Al-Dabbas *et al.* [77]

Table 2 (*continued*)

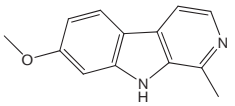
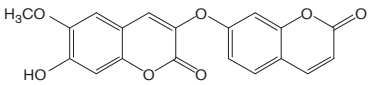
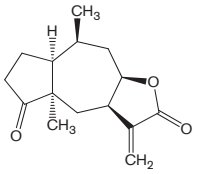
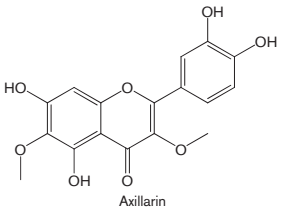
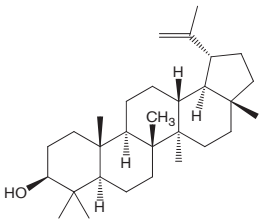
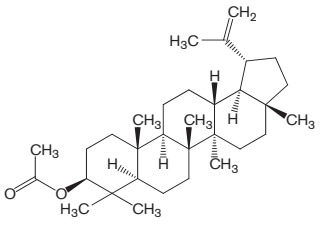
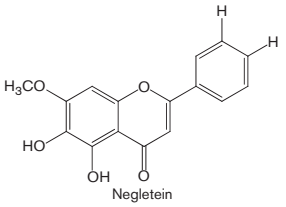
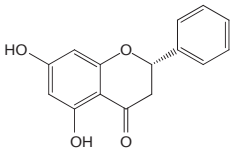
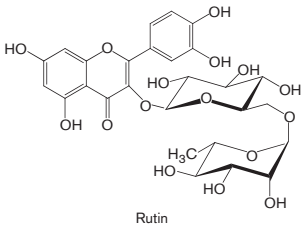
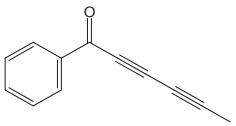
Compound	Chemical class	Plant source	References
 Harmine	Indole alkaloid	*Peganum harmala*	Hamsa *et al.* [59]
 Daphnoretin	Benzopyran	*Thymelaea hirsuta*	Abou-Karam *et al.* [75]
 5,10-epi-2,3-Dihydroaromatin	Guaianolide sesquiterpene	*Pulicaria crispa*	Stavri *et al.* [64]
 Axillarin	*O*-Methylated flavonol	*P. crispa*	Al-Yahya *et al.* [65]
 Lupeol	Triterpenoid	*Centaurea eryngioides*	Sarg *et al.* [53]
 Lupeol acetate	Triterpenoid	*C. eryngioides*	Sarg *et al.* [53]
 Negletein	Flavonoid	*C. eryngioides*	Sarg *et al.* [53]

Table 2 (*continued*)

Compound	Chemical class	Plant source	References
 Pinocembrin	Flavonoid	*C. eryngioides*	Sarg *et al.* [53]
 Rutin	Flavonol glycoside	*Hammada scoparia*	Author not specified [57]
 Capillin	Diacetylenephenyl ketone	*Artemisia monosperma*	Whelan and Ryan [44]

Saponin fractions of *Q. saponaria* (Molina) are cytotoxic against cancer cells *in vitro*, but are too toxic for parenteral use. Interestingly, the toxic effect is abolished in the gastrointestinal tract. A novel approach abolishes the toxic effect by converting *Q. saponaria* fractions into stable nanoparticles through the binding of *Q. saponaria* to cholesterol. Two fractions of *Q. saponaria* were selected for particle formation: one with an acyl chain (ASAP) was used to form killing and growth-inhibiting (KGI) particles and the other without the acyl chain (DSAP) was used for blocking and balancing effect (BBE) particles. KGI exhibited significant growth-inhibiting and cancer cell-killing activities in nine of 10 cell lines, whereas BBE was demonstrated in only one cell line. In the monoblastoid lymphoma cell line U937, low concentrations of KGI (0.5 and 2 μg/ml) induced an irreversible exit from the cell cycle, differentiation measured by cytokine production, and eventually programmed cell death (apoptosis). Compared with normal human monocytes, the U937 cells were 30-fold more sensitive to KGI. The nontoxic BBE blocked the cell-killing effect of KGI in a concentration-dependent manner [67].

Q. saponaria 21, another fraction derived from the bark of *Q. saponaria*, significantly augmented clinical antibody and T-cell responses to vaccine antigens against a variety of infectious diseases, as well as against degenerative disorders and cancers, further highlighting the potential of saponin adjuvants from Quillaja in cancer therapy [68]. Further, the Quillaja saponin adjuvant Quil A and its *Q. saponaria* 21 derivative stimulate both the Th1 immune response and the production of cytotoxic T-lymphocytes against exogenous antigens [70].

The saponin fraction *Q. saponaria* 21 from *Q. saponaria* is a potent immunological adjuvant when mixed with keyhole limpet hemocyanin conjugate vaccines, as well as with other classes of subunit antigen vaccines. The *Q. saponaria* 21 adjuvant is composed of two synthetic isomers that include the apiose and xylose forms in a ratio of 65 : 35, respectively. A study describes in detail in-vivo immunological evaluations of these synthetic constituents, using the GD3-KLH melanoma antigen. It demonstrates that the adjuvant activity of *Q. saponaria* 21 is present in the above-mentioned two principal isomeric forms, but not in trace contaminants within the natural extracts, laying a foundation for future exploration of structure–function correlations to enable the discovery of novel saponins with increased potency, enhanced stability, and attenuated toxicity [69].

Two saponins were isolated from the seed pods of the desert legume plant *Acacia victoriae*, a tree growing in western and mid-Australia. The two compounds exhibited potent cytotoxicity (apoptosis) against human T-cell leukemia *in vitro* [36].

Antitumor effects of desert plants not containing saponins

Nordihydroguaiaretic acid is a naturally occurring lignan mainly isolated and commercially produced from the desert creosote bush (*Larrea divaricata* Cav. or *Corillea tridentate*), widely found in the border zone of southern USA and northern Mexico. Extensive research has demonstrated that nordihydroguaiaretic acid and its synthetic analogues are potentially useful in treating cancer and other diseases. Remarkably, terameprocol, a

tetra-*O*-methyl derivative of nordihydroguaiaretic acid, is in phase I/II clinical trials as an anticancer agent. A recent review details the chemical synthesis and bioactivities of nordihydroguaiaretic acid and its structurally related derivatives possessing anticancer bioactivities [58].

Essential oils steam-distilled from the root of *Anemopsis californica*, a desert plant growing in the southwestern region of the US and northern Mexico, inhibited the growth of AN3CA and HeLa cell lines with IC_{50} values of 0.056 and 0.052% v/v, respectively. The three most abundant compounds present in the oil (namely, thymol, piperitone, and methyleugenol) also inhibited cell growth when tested independently for growth-inhibitory activity against AN3CA and HeLa cells *in vitro*. This study supports extensive ethnological uses of this plant for treating uterine cancer [40].

Cytotoxic activity was exhibited by iridoids, bioactive compounds in the roots and rhizomes of plants belonging to the genus *Valeriana* (Valerianaceae). Plants of this genus growing in the Sonoran Desert, especially *Valeriana officinalis*, are widely used as sedatives in phytomedicine. Iridoids in herbal supplements containing *Valeriana* are known to be the active ingredients. Iridoids are known to be inhibitors of cell migration, recognized as one of the key targets for the discovery and development of new and effective anticancer drugs [76].

Over 500 extracts of Sonoran Desert plant-associated fungi were screened in an effort to discover small-molecule inhibitors of heat shock protein 90 (HSP90). Antiproliferative activity of the active compounds was determined using breast cancer cell line MCF-7. Radicicol and monocillin I were evaluated in a solid-phase competition assay for their ability to bind HSP90 and to deplete cellular levels of two known HSP90 client proteins with relevance to breast cancer, estrogen receptor, and the type 1 insulin-like growth factor receptor. An effective strategy is claimed for the discovery of natural product-based HSP90 inhibitors with potential anticancer activity [80].

Ammopiptanthus mongolicus (Leguminosae) is a plant distributed in the northwestern Gobi and desert areas of China. Its environments involve seasonally extreme drought and temperatures, extraordinarily high UV radiation, and poor soil qualities with high salinity. *A. mongolicus* remains evergreen for all four seasons, and is known to contain extraordinary concentrations of antioxidants. It has been traditionally used in anti-inflammatory, anti-infectious, and for pain-killing medicines. A patent provides information on a new anticancer medicine using *A. mongolicus* and an *A. mongolicus* lipid to inhibit liver cancer, supporting traditional Chinese medicine precepts [39].

Fractionated extracts of *Calligonum comosum* (Polygonaceae), an Egyptian desert plant, were tested for their anticancer activity using Ehrlich ascites, brine shrimp, and antioxidant assays. Ethyl acetate fractions proved to be the most active in all assays [52].

Potential anticancer agents from rhizosphere fungi of Sonoran Desert plants, such as *Ambrosia ambrosoide*, were identified and their molecular structures were established. Two compounds, terrequinone A and terrefuranose, displayed selective cytotoxicity against cancer cell lines compared with the normal fibroblast cells [38].

Antiproliferative and apoptotic properties of extracts derived from the aerial parts of *Pituranthos tortuosus* have been reported using two leukemia cell lines, namely, L1210 and K562. The results revealed that all extracts exerted a significant cytotoxic effect on these cell lines, and the effect was greater in the presence of human K562 chronic myelogenous leukemia cells [62].

The essential oil of *P. tortuosus* extracted using three different methods was tested for its cytotoxic activity on three human cancer cell lines, namely, liver cancer cell line (HepG2), colon cancer cell line (HCT116), and breast cancer cell line (MCF7) [63]. The oil, obtained by a simultaneous hydrodistillation and solvent extraction, showed the most potent activity against the three human cancer cell lines, with IC_{50} values of 1.67, 1.34, and 3.38 μg/ml against liver, colon, and breast cancer cell lines, respectively. Also, significant cytotoxicities were observed of terpinen-4-ol, sabinene, γ-terpinene, and β-myrcene isolated from this extract.

Selected desert plants demonstrated strong cytotoxicity against cultured melanoma cell lines [81]. In another study, 34 of 63 species showed significant inhibitory effects against cervix epithelial carcinoma cells (HeLa) and mouse fibroblast cells (3T3). Also, nine of these active extracts were significantly less toxic to noncancerous mouse fibroblast cell line (3T3) than to cancer cells. This study was conducted to evaluate the potential benefits of using ecology-based theories of plants' chemical defense systems when screening plants for pharmacological activity. It used plant growth patterns (e.g. annual, herbaceous perennial, woody perennial, and evergreen) to suggest plant species that produce beneficial biologically active secondary metabolites. As predicted, using the 'ecology-based approach', the average percent cancer inhibition of extracts from evergreen species and woody perennials was significantly higher compared with the other growth forms [82].

The genus *Commiphora* of the Burseraceae family includes over 150 species and is mainly distributed in East Africa, Arabia, and India. The resinous exudates of these plant species were found to be of significant biological value for their cytotoxic, anti-inflammatory, and antimicrobial effects, and have been used in dentistry for endodontic therapy and temporary fillings, antiseptics, soaps, and

deodorants. Two sesquiterpenoids were isolated from the resinous exudates of *Commiphora opobalsamum* (also known as Mecca myrrh and as Balsam of Gilead), and shown to inhibit proliferation of hormone-independent prostate cancer cell lines in a concentration-dependent manner, whereas normal cells were unaffected [54].

A cycloartane-type triterpenoid, an aliphatic alcohol glycoside, eudesmane-type sesquiterpenoid, and a guaiane-type sesquiterpenoid were isolated from the resinous exudates of *Conmmiphora opobalsamum*, along with six known sesquiterpenoids. The isolated compounds were tested against human prostate cancer cell lines PC3 and LNCaP. Some of the isolated compounds showed moderate antiproliferative effects on human prostate cancer cell lines, with IC_{50} values ranging from 5.7 to 23.6 μmol/l; they were also able to inhibit the expression of androgen receptor in LNCaP cells. The six sesquiterpenoids were inactive in the bioassays [55].

A study evaluated the cytotoxic activities of extracts derived from *V. iphionoides*, a plant growing in arid and semiarid zones, in which fractions of varying polarities were separated and tested for their cytotoxic effects against human leukemia cells, radical scavenging activity, and antibacterial activity. It was found that the less polar fractions exhibited the highest cytotoxicity against leukemia cell proliferation [77].

Recently, we observed a significant antitumor effect of an aqueous extract of *V. iphionoides* against HepG2 human hepatocellular carcinoma cells (unpublished study). An aqueous extract of another desert plant *Achillea fragrantissima* showed a similar cytotoxic effect in HepG2 cells (unpublished study).

Argan oil obtained from the seeds of *Argania spinosa*, a tree endemic to semidesert zones in southwestern Morocco, is a rich source of linoleic and oleic acids (37 and 45%, respectively) and minor compounds (tocopherols, polyphenols, sterols, carotenoids, xanthophylls, and squalene). The antiproliferative effects of polyphenols and sterols extracted from the virgin argan oil were tested on three human prostatic cell lines (DU145, LNCaP, and PC-3). Polyphenols and sterols of virgin argan oil exhibited dose-dependent cytotoxic effects and antiproliferative actions on the three aforementioned cell lines [41,42].

Teucrium polium, distributed in arid, semiarid, and nonarid zones in the Middle East and southern Europe, has been used as a medicinal plant for more than 2000 years for treating many diseases, including abdominal pain, indigestion, and diabetes. The effect of *T. polium* plant extracts on human metastatic prostate cancer cells was examined on selected parameters in PC3 and DU145 prostate cancer cell lines. The results indicate that the *T. polium* plant extract inhibits cell proliferation and induces S phase cell cycle arrest and reduction of the G0–G1 phase, while in parallel inducing differentiation and suppressing cell invasion and motility in PC3 and DU145 cancer cells relative to untreated cells. Expression patterns of E-cadherin and catenins are simultaneously relocalized. The molecular pathway analysis of the *T. polium* plant extract shows that it inhibits the phosphorylation of β-catenin through Src dephosphorylation, and consequently shifts its role from a transcriptional regulator to a cell–cell adhesion molecule. Thus, the *T. polium* plant extract inhibits signaling pathways that regulate the E-cadherin/catenin complex and possibly other cell–cell adhesion genes by β-catenin alteration, suggesting therapeutic potential against metastatic disease [73].

The effect of the methanolic extract of *T. polium* (Me-TP) on the cytotoxic and apoptotic activity of anticancer drugs of vinblastine, vincristine, and doxorubicin *in vitro* was tested in Skmel-3, Saos-2, SW480, MCF-7, KB, EJ, and A431 cell lines. The vincristine/Me-TP, vinblastine/Me-TP, and doxorubicin/Me-TP combinations showed a strong synergistic effect in cell growth inhibition. Similar results were observed by the colony formation assay. Furthermore, the combinations of vincristine/Me-TP and vinblastine/Me-TP resulted in a massive apoptosis (> 80%) compared with the effect of individual drugs (0–3%). Me-TP reduced the cytotoxic effects of vincristine and vinblastine toward the human fibroblasts, suggesting the potential of Me-TP as an effective and safe chemosensitizing agent in cancer therapy [74].

Retama raetam (Papilionaceae) is a desert shrub that grows mainly in countries bordering the eastern Mediterranean. The in-vitro antioxidant and cytotoxic activities of the methanol extracts of leaves and seeds of *R. raetam* (subspecies gussonei) showed good cytotoxic activity against the COR-L23 (large cell lung carcinoma) cell line [71].

Peganum harmala is an arid zone perennial plant used in folk medicine for anticancer therapy. In-vitro and in-vivo studies have demonstrated the antiangiogenic activity of harmine, a β-carboline alkaloid present in this plant. Intraperitoneal administration of harmine at 10 mg/kg body weight of C57BL/6 mice injected with B16F-10 melanoma cells showed significantly decreased tumor directed capillary formation and vascular endothelial growth factor, nitric oxide, inducible nitric oxide synthase, cyclooxygenase-2, metalloproteinases and proinflammatory cytokines and factors, including nuclear factor-kappaB, cAMP responsive element binding protein, and cyclic AMP-dependent transcription factor-2, while increasing antitumor factors, such as IL-2 and tissue inhibitor metalloprotease [59]. Furthermore, a patent describes the use of a preparation containing hydrochloric harmaline in treating gastric cancer, esophageal carcinoma, digestive tract tumor, lymphoma, and pancreatic carcinoma [60]. The methanol extract of the alkaloids harmine and harmaline, both derived from the seeds of *P. harmala* L., inhibited the growth of three human cancer cell lines: UACC-62 (melanoma), TK-10 (renal), and MCF-7 (breast) [61].

The essential oil of *Artemisia campestris* and the ethanol–water, hexane, and water extracts of *A. campestris* and *Thymelaea hirsuta*, desert plants collected in southern Tunisia, were investigated for their antioxidant (DPPH, ABTS, and β-carotene methods) and antitumor growth inhibition of human colon cancer HT-29 cells. The *A. campestris* extracts exhibited antitumor activity ranging from 19.5% for essential oil to 64.4% of negative control growth for an aqueous infusion extract, but not for the hexane extract. With *T. hirsuta*, hexane and ethanol–water but not the infusion extract also exhibited antitumor activity (58.2 and 65.5% of control growth, respectively). The ethanol–water extracts of *A. campestris* showed higher antioxidant activity, polyphenol, and flavonoid contents than those of *T. hirsuta* [43]. These results indicate a positive correlation between the antitumor activity and the antioxidant activity, and also with the levels of polyphenols and flavonoids.

T. hirsuta is a desert shrub distributed in the southern part of Israel and in arid zones all over the Middle East. A study aimed to find inhibitors of oncogene product enzyme activity as a prescreen for potential cancer chemopreventive agents. Daphnoretin, a dicoumaryl ether from *T. hirsuta* root, inhibited the ErbB oncogene product, the tyrosine-specific protein kinase of human epidermal growth factor receptor ($IC_{50} = 97.5$ μmol/l). Daphnoretin demonstrated moderate cytotoxicity ($IC_{50} = 21–114$ μmol/l) only in rapidly proliferating cultured mammalian cells [75].

A study of the asteraceous herb *Pulicaria crispa* (Forssk.) Oliv. resulted in the characterization of three guaianolide sesquiterpenes: 2α,4α-dihydroxy-7α*H*,8α*H*,10α*H*-guaia-1(5), 11(13)-dien-8β,12-olide, 1α,2α-epoxy-4β-hydroxy-5α*H*,7α*H*, 8α*H*,10α*H*-guaia-11(13)-en-8β,12-olide, and 5,10-epi-2, 3-dihydroaromatin. The structures were assigned on the basis of extensive one-dimensional and two-dimensional NMR experiments. The third compound exhibited cytotoxicity (IC_{50} of 5.8 ± 0.2 μmol/l) in a human bladder carcinoma cell line, EJ-138 [64].

The sesquiterpene lactones, 2α-hydroxy-5α,6α-epoxy-alantolactone and axillarin, were isolated from *P. crispa*. Both compounds exhibited antineoplastic and cytotoxic activity, respectively [65].

Salvadora persica (Salvadoraceae) is a Sudanese tree, widespread in desert flood plains and grassy savannah. It is found where ground water is readily available, on river banks, on the perimeters of waterholes, in seasonally wet sites, and along drainage lines in arid zones. The tree is able to tolerate a very dry environment, with a mean annual rainfall of less than 200 mm. The toxic effects of four dilutions of *S. persica* and chlorhexidine gluconate (CHX) mouthwashes on KB, Saos-2, J744 A1, and gingival fibroblast cells were evaluated by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay. The effect of fetal calf serum (FCS) components on the cytotoxicity of these mouthwashes was also investigated. The results indicated that *S. persica*, at concentrations higher than 0.1%, exerted a very significant cytotoxic effect on all cell lines. CHX, at a concentration of 0.001%, exerted toxic effects only on gingival fibroblasts; concentrations higher than 0.001% were required to produce significant cell death in the other cell lines. At all concentrations under study, both *Persica* and CHX exerted significantly greater cytotoxic effects in the absence of FCS than in its presence (i.e. in control culture medium). The toxicities of both mouthwashes were attenuated in the presence of FCS (10%). These results indicate that both the plant and the CHX mouthwashes are toxic to macrophage, epithelial, fibroblast, and osteoblast cells in a concentration-dependent manner [72].

Centaurea eryngioides (Compositae) is a desert plant that grows in the Israeli Negev and the Judean Desert. Column chromatography of the light petroleum extract of *C. eryngioides* yielded lupeol acetate, lupeol, saturated hydrocarbon, a sitosterol mixture, and β-sitosterol glucoside. The chloroform extract yielded the flavonoids negletein, negletein-6-glucoside, pinocembrin, and pinocembrin-5,7-diglycoside. Gas–liquid chromatography of the methylated fatty acids revealed the presence of 16 fatty acids. Analysis of the total hydrocarbons by gas–liquid chromatography showed the presence of 18 different hydrocarbons. Investigation of the fractionated extracts indicated promising antimicrobial and antitumor activities [53].

Calotropis procera (Asclepiadaceae) is a woody, broad leaf evergreen coarse shrub distributed in arid regions of the Caribbean, Central America, South America, Africa, India, and Israel, mainly appearing on plains and in the highlands. This plant, also referred to as 'The Apple of Sodom', has been used especially in traditional folk medicine because of pharmacologically active compounds in its roots, bark, leaves, and especially its latex, exuding from damaged leaves. Latex of *C. procera* is a source of pharmacologically active proteins, some with anticancer activity. Laticifer proteins (LP) from *C. procera* significantly reduced tumor growth and augmented the survival time of animals for up to 4 days. Tumor growth-inhibitory activity was lost when the LP fraction was subjected to proteolysis, acidic treatment, or pretreated with iodoacetamide. However, LP retained its inhibitory activities on the growth of sarcoma 180 after heat treatment, suggesting that heat-stable proteins are involved in tumor suppression. LP completely eliminated the 5-fluorouracil-induced depletion of leukocytes in mice even when given orally. The active proteins were recovered in a single fraction by ion exchange chromatography and still exhibited the ability to control sarcoma cell proliferation [48].

The antitumor potential of root extracts of *C. procera* and its possible mechanism against HepG2 cancer cells were also explored. Three extracts were cytotoxic, one of

which (10 μg/ml) showed the strongest effect on HepG2 48 h following treatment. Extract-treated cells exhibited typical morphological changes of apoptosis. Flow cytometric analysis clearly demonstrated that *C. procera* root extracts initiated apoptosis of HepG2 cells through cell cycle arrest at the S phase, thus preventing cells from entering the G2/M phase. The results of the study indicate that the root extracts of *C. procera* inhibit the proliferation of HepG2 cells by apoptotic and cell cycle disruption-based mechanisms [49]. Recently, the cardiotonic steroid UNBS1450 01 (derived from 2-oxovoruscharin 02) from *C. procera* was shown to exert anticancer activity [50].

The cytotoxic potential of organic stem extracts from *C. procera* was evaluated against cancer cell lines by an MTT assay [51]. Subsequently, samples considered cytotoxic were tested for antimitotic activity on sea urchin egg development and for in-vivo antiproliferative activity in mice bearing a sarcoma 180 tumor. Among the five extracts (hexane, dichloromethane, ethyl acetate, acetone, and methanol), ethyl acetate and acetone extracts displayed higher cytotoxic potential against tumor cells, with IC_{50} values ranging from 0.8 to 4.4 μg/ml, whereas a methanolic extract was weakly cytotoxic. Cytotoxic extracts also exhibited cell division inhibition capacity. In-vivo antitumor assessments of ethyl acetate- and acetone-treated animals showed tumor growth inhibition ratios of 64.3 and 53.1%, respectively, with reversible toxic effects on the liver and kidneys.

Hammada scoparia (Chenopodiaceae) is a shrub distributed in the deserts of northern Africa and southwestern Asia. A patent demonstrated the use of heterosidic flavonoid derivatives from the leaf extracts of this plant, particularly rutin, in treating stem cell cancer, specifically acute myeloid leukemia, and preventing solid tumor metastasis. A specific cytotoxic activity of *H. scoparia* leaf extract against adherent leukemic cells was demonstrated. Also, the cytotoxicity toward leukemic cells induced by daunorubicin treatment was strongly increased by the *H. scoparia* extract, both in suspension and under adherent conditions [57].

The effects of capillin, a constituent of *Artemisia monosperma*, a plant that grows in both desert and Mediteranean climates, were investigated on four human tumor cell lines: colon carcinoma HT29, pancreatic carcinoma MIA PaCa-2, epidermoid carcinoma of the larynx HEp-2, and lung carcinoma A549. Capillin (1–10 μmol/l) inhibited cell proliferation and simultaneously decreased macromolecular synthesis in a dose-dependent and time-dependent manner. Coincubation with L-buthionine sulfoximine augmented the efficacy of capillin. Capillin modulated glutathione levels, accumulated cells in the S + G2/M-phase of the cell cycle, and induced cell death and DNA fragmentation [44].

Clustered genes have been cloned and functionally characterized for the biosynthesis of radicicol from the fungus *Chaetomium chiversii*, an endophyte of Mormon tea (*Ephedra fasciculata*), a perennial shrub growing in the Sonoran Desert of Arizona. Radicicol, a resorcylic acid lactone polyketide, is a nanomolar inhibitor of the evolutionarily conserved chaperone HSP90. Depletion of HSP90 leads, in turn, to a combinatorial blockade of multiple cancer-causing pathways. These fungal polyketides are of interest for therapeutic areas as diverse as the treatments of cancer, and neurodegenerative and infectious diseases [56]. Here is a remarkable example of how harsh thermal conditions prevailing in the desert trigger the production of secondary metabolites, such as radicicol, capable of indirectly inducing cancer inhibition.

The preparation of the anticancer Chinese herbal medicine BG-104 was described, in which natural plants and seeds (Bezoar Bovis, Kadinum, Rhei Rhizom, Hoelen, Arecae seed, and the Kalahari Desert harvested pedaliaceae), are heated with far infrared rays of wavelength 4–14 μm and fermented using 'Koji' (the fungus *Aspergillus oryzae*). BG-104 significantly potentiates the ability of human leukocytes to induce natural killer cells and superoxide dismutase [83]. The clinical efficacy of the herbal medicine was studied on 50 patients with advanced breast cancer who had not responded to other treatments and on those who had been classified as stage III or IV by the tumor modes metastasis (TNM) classification. Patients treated with BG-104 and not in combination with chemotherapy or radiotherapy showed a higher surviving rate: the 3-year survival rate was 85%, the 4-year survival rate was 75%, and the 5-year survival rate was 75%. The study also suggests a mechanism of action for BG-104 [84].

Conclusion and future perspectives

Although the role of natural products as a source for remedies has been recognized since the beginning of mankind, only a few folk medicinal plants have been scientifically evaluated for their pharmacological activities. The many chemicals of plant origin with therapeutic attributes still remain to be explored. Desert plants remain an almost virgin field of exploration, and a promising one too due to the high concentration of therapeutic components present in many of them.

The large numbers of studies summarized in this review indicate the connection between the concentration of components with therapeutic attributes in desert plants and the harsh environmental conditions under which they live [41,42]. Experimental results show a positive correlation between antitumor activity and antioxidant activity, and of these two activities with the levels of polyphenols and flavonoids [43]. Heat and radiation stresses are linked to an enhanced susceptibility to oxidation, successfully being resisted by the efficient antioxidative systems evolved in desert plants. It has

been suggested that plant species living in extremely stressful environments may become an abundant natural resource of strong antioxidants [1]. It is believed that external desert conditions trigger biological pathways that might be effective in the production of components with therapeutic potential. In a specific case, the biosynthesis of a cancer preventive chemotype, such as radicicol, is suggested to be heat induced [56].

Also, water scarcity induces the production of therapeutic biochemicals in desert plants. For example, the structural matrix in many xerophytes also contains, in addition to the usual polyuronides, substantial amounts of steroids and triterpene saponins, aiding in the storage and conservation of water and in surviving severe weather conditions, but which are also known as cancer preventive agents [29].

In summary, the studies presented in this article unveil the extraordinary therapeutic potential of desert plants. As the incidence of major types of cancer continues to increase, a shift in approach is needed toward harnessing the capabilities of desert plants in fighting cancer.

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Conflicts of interest

There are no conflicts of interest.

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