# Cancer Preventive and Curative Attributes of Plants of the Cactaceae Family: A Review

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## Abstract

The ever-increasing occurrence of cancer and the severe side effects and limited efficacy of current cancer chemotherapy based on chemical drugs shift the attention toward drugs of plant origin. The Cactaceae family comprises more than 1500 species, but until recently only a few of them have been tested for their chemopreventive and anticancer attributes, leaving a wide unexplored area still waiting for researchers to investigate. Considering this fact, and also the promising results obtained with the relatively few plants of this family already tested, it should justly be expected that some plants of the Cactaceae family yet unexplored might possess outstanding anticancer attributes, exceeding those displayed by the plants already tested. This review presents *in vitro* and *in vivo* experimental evidence on cancer chemopreventive and therapeutic potential of bioactive phytoconstituents and extracts derived from cactus plants. It also examines the underlying biochemical and molecular mechanisms involved in the antineoplastic effects of plants of the Cactaceae family. Current limitation and future directions of research towards effective use of cacti to develop efficient and side effect-free future cancer-preventive and anticancer drugs are also discussed.

## Abbreviations

| | |
|---|---|
| $AFB_1$: | aflatoxin $B_1$ |
| B[a]P: | benzo[a]pyrene |
| CDDP: | *cis*-diamine dichloroplatinum |
| CME: | cactus mixture extract |
| CTX: | cyclophosphamide |
| Cyt. *c*: | cytochrome *c* |
| DMBA: | 7,12-dimethylbenz[a]anthracene |
| 4-HPR: | N-(4-hydroxyphernyl) retinamide |
| HSP27: | heat shock protein 27 |
| HSP70: | heat shock protein 70 |
| i. p.: | intraperitoneal |
| MDA: | malondialdehyde |
| NF-κB: | nuclear factor-kappaB |
| NO: | nitrogen monoxide |
| PARP: | poly (ADP) ribose polymerase |
| PC: | protein carbonyls |
| RBC-CaR: | RBC-cancer cell immune adherence |
| RFER: | RBC immune adherence enhance factor |
| RFIR: | RBC immune adherence inhibitor factor |
| ROS: | reactive oxygen species |
| SOD: | superoxide dismutase |
| TPA: | 12-*O*-tetradecanoylphorbol-13-acetate |
| VEGF: | vascular endothelial growth factor |

## Introduction

Ample evidence exists of the steadily increasing occurrence of cancer in Western societies being the result of environmental factors and of lifestyle [1]. For example, a recently published article suggests that cancer is practically a man-made disease, steadily growing since the beginning of the industrial revolution in the mid-19th century but rarely having been witnessed in the ancient world or in current non-modern (frequently referred to as "primitive") societies [2]. Targeting both lifestyle and environment, thus adopting a preventive approach, seems to be the preferred and most logical way to cope with the problem. However, current cancer research focuses mainly on curing the disease, while it should preferably be based on developing drugs of plant origin because, unlike their synthetic chemical counterparts, their predisposition to produce severe side effects is small.

Plants of the Cactaceae family are mostly desert and semidesert habitants, which, owing to harsh

environmental stress conditions (water scarcity, strong radiation, temperature differences, and poor soil) are conceived to have developed highly effective defense systems, allowing them to successfully cope with the environment. These defense systems are made of phytochemicals, such as alkaloids, flavonoids, terpenes, and tannins, already shown to exhibit remarkable bioactivities against human diseases such as cancer [3,4] and diabetes [5].

The fact that herbs and plant-derived products lack much of the toxicity present in synthetic chemicals enhances their appeal for treating cancer and for long-term preventive strategies. Cactus pears and cladodes (modified stems) contain, among other components, pectin, carotenes, betalains, ascorbic acid, and quercetin derivatives, all of which are known to possess antioxidant properties, marking them a potential source for anticancer and cancer preventive drugs. Emerging studies indicate remarkable anticancer activities displayed by cactus pear extracts. Deprived of toxic effects, cactus-derived components can be easily used, for example, as dietary supplements in normal and high-risk populations for cancer [6]. Cactus pears have been used by Native Americans for centuries as a dietary supplement, and these ethnic groups show lower cancer rates when compared to white and African Americans [7–9]. This historical fact is further confirmed by experimental results, such as shown in this review, indicating the potential of plants of the Cactaceae family for inhibiting the growth of various cancer cells and inducing anticancer biological effects *in vivo*.

The aim of this article is to review the experimental work performed to date on plants of the Cactaceae family in cancer research. To the best of our knowledge this attempt is the first of its kind. Various pure compounds isolated from cacti are presented in **Table 1**. The anticancer activities of these compounds as well as of extracts from plants belonging to the Cactaceae family are exhibited *in vitro* (**Table 2**) and *in vivo* (**Table 3**). **Fig. 1** displays pictures of cacti endowed with chemopreventive and anticancer properties.

## Search Methodology

The purpose of this review has been to provide the interested reader with a broad view of the research work performed up-to-date on the subject. To achieve this goal, the scientific search engine "SciFinder" was found to be an extremely useful tool, as it retrieves information from both MEDLINE and CAPLUS data bases. In some cases, the original articles were obtained and carefully examined. In other cases, only the abstracts have been used. As the amount of work performed on the subject is not very large, we have tried our best to incorporate into this article any work located in the scientific literature adding new information.

## Antitumor effects of extracts and pure components derived from cacti

### Genus *Opuntia*

*Opuntia*, a genus of the Cactaceae family, includes about 200 species and is comprised solely of prickly pear cacti. The stems of these perennial cacti are composed of flattened segments, intensely green and covered in bristles and spines according to the variety. The flowers are bright yellow, cream, or gold in color and are found along the margins of most mature upper segments. The petals of the flowers have a waxy texture, and sometimes the centers and sepals of the flowers are reddish in color. The fruits vary greatly in taste, size, and edibility, developing in color from green to red, pink, and orange; they are three to five centimeters long and full of small marble-like seeds. The plant thrives in full sun.

The best known species of this genus is the xerophyte cactus *Opuntia ficus-indica* (L.) Mill. (**Fig. 1 A**), commonly called "Indian fig", which attracts significant interest as a nutritional and pharmacological power source. This tree-like cactus is widespread throughout Central and South America, Australia, South Africa, and the whole Mediterranean area [10]. The great number of potentially active nutrients and their multifunctional properties make the juice of the cactus pear (the fruit of *O. ficus-indica*, also referred to as "prickly pear") a perfect candidate for the production of health-promoting food and food supplements. Health benefits and medicinal and nutritional use of the cactus pear, including reduction in the risk of cancer, were reviewed [6, 11, 12].

*In vitro studies*: Juices extracted from nine prickly pears (belonging to genus *Opuntia*) were found *in vitro* to diminish the viability of prostate, colon, mammary, and hepatic cancer cells without affecting normal fibroblast viability (**Table 2**). The differences in anticancer effects among the tested juices were attributed to variations in their content of phytochemicals, such as flavonoids and betalains, compounds known to prevent oxidative stress and cancer [13].

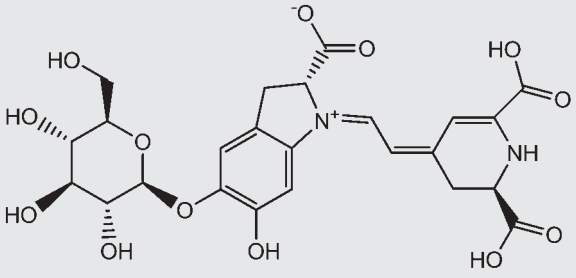
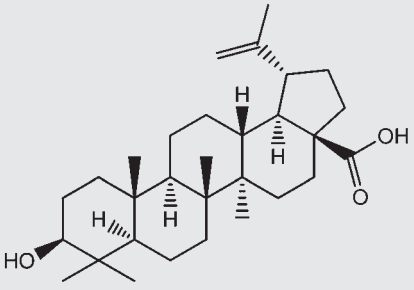
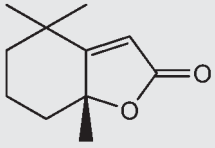
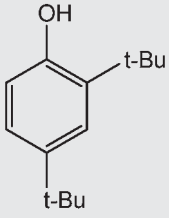
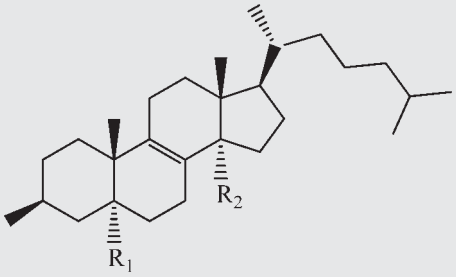
Aqueous extract of the Arizona cactus pear were used by Zou et al. [6] to treat immortalized ovarian and cervical epithelial cells, as well as ovarian, cervical, and bladder cancer cells. Cells exposed to Arizona cactus aqueous pear extracts exhibited a significant increase in apoptosis and growth inhibition in both immortalized epithelial cells and cancer cells in a dose- and time-dependent manner. It also affected the cell cycle of cancer cells by increasing G1 and decreasing G2 and S phases.

An aqueous CME derived from the Arizona cactus pear reduced the growth of ovarian cancer cells by inducing apoptosis *in vitro*. Treating normal, immortalized ovarian and ovarian cancer cells (OVCA420 and SKOV3, respectively) with 5 and 10% CME exhibited a dramatic increase of ROS. Greater levels of DNA fragmentation, together with a perturbed expression of apoptotic-related genes, namely Bax, Bad, caspase-3, Bcl-2, p53, and p21 and ROS-sensitive genes, such as NF-κB and c-jun/c-fos, were observed in the treated cancer cells, and the NF-κB and p-SAPK/JNK expressions were decreased after three days of treatment. The CME significantly induced apoptosis in cancer cells, attributed to the accumulation of intracellular ROS, which may activate a cascade of reactions leading to apoptosis [14].

Betalains are water-soluble nitrogenous vacuolar pigments present in flowers and fruits of many caryophyllales with potent antioxidant, anti-inflammatory, and anticarcinogenic properties [15]. Betanin (**Table 1**), the most abundant phytochemical of all betalains, isolated from the fruits of *O. ficus-indica*, was found to decrease dose- and time-dependent proliferation of K562 human chronic myeloid leukemia cells. The results also indicated that betanin induces apoptosis in K562 cells through alteration of mitochondrial membrane integrity, leading to Cyt. *c* leakage from mitochondria into the cytosol, PARP cleavage, downregulation of Bcl-2, and reduction in the membrane potential [16].

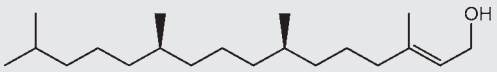
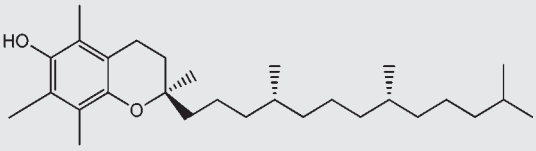
*Opuntia humifusa* (Raf.) Raf. (**Fig. 1 B**), commonly known as the Eastern prickly pear or Indian fig, is a native cactus found in most of eastern North America. It is also widely distributed in the southern regions of the Korean peninsula and known to have bioactive functions and medicinal benefits in the treatment of various diseases such as arteriosclerosis, diabetes mellitus, gastritis,

**Table 1** Structures of anticancer compounds derived from plants of the Cactaceae family.

| Compound | Chemical class | Plant source | Reference |
|---|---|---|---|
|  **Betanin** | Betalains | *O. ficus-indica* | Sreekanth et al., 2007 [16] |
|  **Betulinic acid** | Triterpenoids | *S. stellatus* | Kinoshita et al., 1999 [38] |
|  **Dihydroactinidiolide** | Terpenes | *P. bleo* | Malek et al., 2009 [28] |
|  **2,4-Di-tert-butylphenol** | Substituted phenols | *P. bleo;* *P. grandifolia* | Malek et al., 2009 [28]; Sri Nurestri et al., 2009 [30] |
|  **Peniocerol** ($R_1$ = H, $R_2$ = H) **Macdougallin** ($R_1$ = H, $R_2$ = $CH_3$) | Sterols | *M. geometrizans* | Salazar et al., 2011 [36] |

*continued*

**Table 1** *Continued*

| Compound | Chemical class | Plant source | Reference |
|---|---|---|---|
|  Phytol | Diterpene alcohols | *P. bleo* | Malek et al., 2009 [28] |
|  α-Tocopherol (vitamin E) | Substituted phenols | *P. bleo* | Malek et al., 2009 [28] |

and hyperglycemia. A study investigated total polyphenol and flavonoid contents of the plant's fruit and its anticarcinogenic effects on human breast cancer. Water extracts of the fruit of *O. humifusa* were found to inhibit MCF-7 human breast cancer cell proliferation and to induce G1 arrest [17].

Hexane and ethyl acetate water partitioned extracts of the fruits and stems of *O. humifusa* were tested on U87MG human glioblastoma cells and found to induce both apoptosis and G1 arrest. The number of viable U87MG cells decreased in a concentration-dependent manner following the extract treatment [18].

Three *Opuntia* polysaccharides exhibited remarkable concentration-dependent inhibitory effects on various human cancer cells. The results showed that the medicinal cactus has the best inhibitory effect on ANIP human lung adenocarcinoma cells, the edible cactus has the best inhibitory effect on K562 human chronic myeloid leukemia cells, and another cactus has the best inhibitory effect on HeLa cervical carcinoma cells [19].

*In vivo studies*: The antiproliferative efficacy of *O. ficus-indica* was tested against B[a]P, a widespread environmental genotoxin classified as probably carcinogenic to humans. The aim of the study was to investigate the *in vivo* protective effect of an extract obtained from *O. ficus-indica* cladode against B[a]P using Balb/c mice. The extract exhibited total reduction of B[a]P-induced oxidative damage for all tested markers. It caused apoptosis via inhibition of antiapoptotic proteins Bcl-2 expression and the induction of p53 and Bax expression, thus modulating the p53-dependent apoptotic pathway to restrict the B[a]P toxicity (**Table 3**) [20]. The same investigators also showed that the cladode extract of *O. ficus-indica* induced total reduction of $AFB_1$-induced genotoxicity in mice. The hepatoprotective effect of the extract against aflatoxicosis in mice was attributed to the promotion of the antioxidant defensive system [21]. In an extension of the aforementioned studies, the same extract has been shown to be beneficial in reversing CDDP-induced kidney dysfunction in mice through its antioxidant and antiapoptotic activities [22].

The effect of cactus pear solution on inhibiting tumor growth in mice indicated by tumor size was compared with a synthetic retinoid, 4-HPR, a compound currently being used as a chemopreventive agent in ovarian, cervical, and bladder cancer clinical trials. The inhibitory effect of 4-HPR was found not to be significantly different than that induced by the cactus pear extract solution. The cactus pear extract significantly suppressed ovarian tumor growth in nude mice, increased annexin IV expression (indication of apoptosis) and decreased VEGF expression [6].

*O. humifusa* was investigated for its *in vivo* chemopreventive effect on skin carcinogenesis induced by DMBA and TPA in mice. Significant decrease in the numbers of papilloma and epidermal hyperplasia was observed in mice fed with *O. humifusa*, compared to the control group. The chemopreventive effects of *O. humifusa* on chemical carcinogenesis in the mouse skin are thought to be associated with the reduction of oxidative stress via the modulation of cutaneous lipid peroxidation, enhancement of the total antioxidant capacity, especially in the phase II detoxifying enzyme, and a partial apoptotic influence [23].

### Genus *Pereskia*

*Pereskia* is a genus of about 25 species that do not resemble most other cacti as they have shapely privet-like leaves and thin stems. Their native range are the areas between Mexico and Brazil, often dry forest or thorny scrubs. Some species are epiphytes. However, all of them have cactus-like flowers despite the fact that some species of the *Pereskia* genus do not resemble cacti or succulents. *Pereskia bleo* (Kunth) DC, commonly known as "Pokok Jarum Tujuh Bilah" (in Malay) and "Cak-Sing Cam" (in Chinese) by the locals, is a leafy and spiny shrub known to have many medicinal properties and has been used as a natural remedy in cancer-related diseases, either eaten raw or taken as a concoction brewed from fresh plants. It is believed to have anticancer, antitumor, antirheumatic, antiulcer, and anti-inflammatory properties and has been used as a remedy for the relief of headache, gastric pain, ulcers, hemorrhoids, atopic dermatitis, and for revitalizing the body [24]. The leaf of this plant has been used in Malaysian traditional medicine for the prevention and treatment of breast cancer [25].

*In vitro studies*: The methanol extract of *P. bleo* indicated *in vitro* cytotoxic activity against T-47D breast carcinoma cells with an $EC_{50}$ of 2.0 µg/mL. T-47D cell death elicited by the extract was attributed to DNA fragmentation, a hallmark of apoptosis. Ultrastructural analysis also revealed apoptotic characteristics in the extract-treated cells. RT-PCR analysis indicated increased mRNA expression levels of c-myc and caspase-3 in cells treated with the extract. However, p53 expression was only slightly increased as compared to caspase-3 and c-myc. The results suggested that the methanol extract of *P. bleo* may contain bioactive compound(s)

**Table 2** *In vitro* anticancer effects of extracts derived from and components included in plants of the Cactaceae family.

| Cactus | Fraction/component studied | Cellular effect | Mechanism | $IC_{50}$ | Reference |
|---|---|---|---|---|---|
| *O. ficus-indica*<br>*O. robusta* Amarillo<br>*O. robusta* Gavia<br>*O. robusta* Tapon<br>*O. streptacantha* Cardon<br>*O. violaceae* Moradillo<br>*O. rastrera* Rastrero<br>*O. leucotricha* Duraznillo Blanco<br>*O. leucotricha* Duraznillo Rojo | Prickly pear juice | Diminished the viability of prostate, colon, mammary, and hepatic cancer cells | Antioxidant effects | | Chavez-Santoscoy et al., 2009 [13] |
| *O. ficus-indica* | Aqueous cactus pear extract | Inhibited the growth of TCL-1, HeLa, Me180, IOSE, SKOV3, OVCA420, UM-UC6, T24, and UM-UC9 cells | ↑ G1 phase; ↓ G2 & S phases | | Zou et al., 2005 [6] |
| | | Displayed growth-inhibitory effect in OVCA420 and SKOV3 cells | ↑ Apoptosis; ↑ Bax; ↓ Bcl2, ↑ caspase-3; ↓ NF-κB, ↓ p-/SAPK/JNK; ↑ p53; ↑ p21; ↑ p-AKT | | Feugang et al., 2010 [14] |
| | Betanin | Exhibited antiproliferative effects on in K562 cells | ↑ Apoptosis; ↓ Bcl-2; ↑ caspase; ↑ Cyt. *c*; ↑ PARP cleavage | 40 µM | Sreekanth et al., 2007 [[16] |
| *O. humifusa* | Aqueous fruit extract | Inhibited the proliferation of MCF-7 cells | Induced G1 arrest | | Yoon et al., 2009 [17] |
| | Fruit and stem aqueous extracts | Suppressed the growth of U87MG cells | ↑ Apoptosis; ROS-induced G1 arrest | | Hahm et al., 2010 [18] |
| *P. bleo* (Kunth) DC | Aqueous leaf extract | Exhibited cytotoxic effects in T-47D cells | ↑ Apoptosis; ↑ caspase-3; ↑ c-myc | 2.0 µg/mL ($EC_{50}$) | Tan et al., 2005 [24] |
| | | Inhibited the proliferation of 4 T1 cells | ↑ Apoptosis | | Er et al., 2007 [26] |
| | Methanolic and ethyl acetate extracts | Induced cytotoxicity against KB cells | | 4.5–6.5 µg/mL | Sri Nurestri et al., 2008 [27] |
| | Dihydroactinidiolide | Induced cytotoxicity against HCT116 cells | | 5.0 µg/mL | Malek et al., 2009 [28] |
| | 2,4-Di-tert-butylphenol | Induced cytotoxicity against KB, CasKi, A546, and MCF-7 cells | | 0.81–6 µg/mL | |
| | Phytol | Induced cytotoxicity against KB cells | | 7.1 µg/mL | |
| | α-Tocopherol | Induced cytotoxicity against CasKi, A549, and MCF-7 cells | | 6–7.5 µg/mL | |
| *P. grandifolia* Haw | Hexane extract | Induced cytotoxicity against KB cells | | 5 µg/mL | Sri Nurestri et al., 2009 [30] |
| | Ethyl acetate extracts | Induced cytotoxicity against KB and MCF-7 cells | | 16–20 µg/mL | |
| | 2,4-di-*tert*-butylphenol | Exerted cytotoxicity against KB cells | | 0.81 µg/mL | |
| | Methanolic extract of leaves | Showed cytotoxicity against Saos-2 cells | | | Liew et al., 2012 [31] |
| *H. undatus*;<br>*H. polyrhizus* | Methanolic extracts of peel and flesh | Displayed antiproliferative effects against AGS and MCF-7 cells | | | Kim et al., 2011 [32] |
| | | Exhibited growth-suppressive effects of B16F10 cells | | | Wu et al., 2006 [33] |
| | Methanolic extract of fruits | Inhibited the proliferation of MCF-7 cells | Nitric oxide scavenging | | Jayakumar et al., 2011 [34] |
| *M. geometrizans* | Peniocerol; macdougallin | Induced cytotoxicity against PC-3, K-562, U-251, MCF-7, and HCT-15 cells | | 7.55–24.73 µM | Salazar et al., 2011 [36] |
| *S. stellatus* Riccob. | Betulinic acid; 3-*O*-acetylbetulinic acid | Exerted antitumorigenic activity against HeLa cells | | | Kinoshita et al., 1999 [38] |
| Non-identified cactus | Polysaccharide | Inhibited the growth of SK-MES-1 cells | | | Wu et al., 2012 [44] |

**Table 3** *In vivo* anticancer effects of extracts derived from and components included in plants of the Cactaceae family.

| Cactus | Fraction/component studied | Biological effects | Mechanism | Dose (duration)/route | Reference |
|---|---|---|---|---|---|
| *O. ficus-indica* | Aqueous cladode extract | Protected against B[a]P-induced genotoxicity in BALB/c male mice | ↓ MDA; ↓ catalase; ↓ HSP70; ↓ HSP27; ↑ p53, ↑ Bax; ↓ Bcl-2 | 50 mg/kg (15–30 days); i. p. | Brahmi et al., 2011 [20] |
| | | Reversed $AFB_1$-induced hepatic damage in BALB/c male mice | ↓ MDA; ↓ PC; ↓ HSP70; ↓ HSP27; ↓ p53; ↓ Bax; ↑ Bcl-2 | 50 mg/kg (15–30 days); i. p. | Brahmi et al., 2011 [21] |
| | | Exhibited antigenotoxic effects in CDDP-exposed male BALB/c mice | ↓ MDA; ↓ catalase; ↑ SOD; ↓ p53; ↓ Bax; ↑ Bcl-2 | 50 mg/kg (15–30 days); i. p. | Brahmi et al., 2012 [22] |
| | Aqueous cactus pear extract | Suppressed tumor growth in female BALB/c mice xenografted with SKOV3 cells | ↑ Apoptosis; ↓ VEGF | 0.4 mL/mouse/day (5 days); i. p. | Zou et al., 2005 [6] |
| *O. humifusa* | Cactus fruit powder | Decreased numbers of papillomas and epidermal hyperplasia in DMBA-treated female BALB/c mice | ↑ Apoptosis; ↓ MDA; ↑ SOD; ↑ GST | 1, 3 % (3 weeks); diet | Lee et al., 2012 [23] |
| Non-identified cactus | Polysaccharides from cactus pear | Inhibited the growth of S180 transplanted tumors in mice | ↑ Apoptosis; ↓ MDA; ↑ SOD; ↓ NO | Non-specified | Liang et al., 2008 [45] |
| | | Suppressed the growth of S180 carcinoma and prolonged the survival of H22 tumor-bearing mice | Non-specified | Non-specified | Ji et al., 2004 [46] |
| | | Induced antitumor effect on S180 tumor-bearing mice | ↑ RBC-CaR; ↑ RFER; ↓ RFIR; ↑ sialic acid | Non-specified | Ji et al., 2005 [47] |

causing T-47D breast carcinoma cell death by apoptotic mechanism via the activation of caspase 3 and c-myc pathways [24].

Er et al. [26] found that an aqueous extract from the leaves of *P. bleo* induced a significant antiproliferative activity in a mouse mammary cancer cell line (4 T1) and in a normal mouse fibroblast cell line (NIH/3 T3). An upward trend of apoptosis was observed in both 4 T1 and NIH/3 T3 cells treated with increasing concentrations of the aqueous extracts, and the level of apoptosis observed at all the concentrations of the extract tested was consistently higher than necrosis.

The crude methanol extract of *P. bleo* and its fractionated ethyl acetate extract were found to possess a notably high cytotoxic effect against human nasopharyngeal epidermoid (KB) cells with $IC_{50}$ values of 6.5 and 4.5 µg/mL, respectively. Four compounds isolated from the ethyl acetate fraction of *P. bleo* were identified as phytol, *β*-sitosterol, 2,4-di-*tert*-butylphenol, and vitamin E [27]. In a later study, dihydroactinidiolide, 2,4-di-*tert*-butylphenol, *α*-tocopherol, and phytol were isolated, identified, and their cytotoxicity was tested against five human carcinoma cell lines, namely KB, CasKi, HCT 116, MCF7, and A549. This study confirmed that 2,4-di-tert-butylphenol, isolated from the active ethyl acetate fraction derived from the leaves of *P. bleo*, possessed remarkable cytotoxic activity against KB cells, with an $IC_{50}$ value of 0.81 µg/mL, while each of the other isolated components displayed cytotoxicity of around 6 µg/mL against KB, and roughly the same value against the other cell lines. Furthermore, unlike doxorubicin, a currently used cytostatic drug for the treatment of cancer, crude extracts and pure components derived from *P. bleo* have low toxicity against normal MRC-5 cells, indicating better selectivity than that of doxorubicin [28].

The leaves of *P. grandifolia* Haw., another Cactaceae plant of the genus *Pereskia*, commonly known as "Jarum Tujuh Bilah" in Malaysia, have been traditionally used as a natural remedy in folk medicine by the locals, and their high antioxidant potential was confirmed [29]. The hexane fraction of *P. grandifolia* induced a remarkable cytotoxic effect against KB cells with $IC_{50}$ values of 5.0 µg/mL, while the ethyl acetate fraction displayed a high cytotoxic effect against both KB and MCF-7 cells with $IC_{50}$ values of 16.0 and 20.0 µg/mL, respectively. 2,4-di-*tert*-butylphenol, isolated from the active ethyl acetate fraction of this plant, possessed very remarkable cytotoxic activity against KB cells, with an $IC_{50}$ value of 0.81 µg/mL [30].

Crude methanol extract of the leaves of *P. grandifolia*, a plant also used in traditional Chinese medicine, exhibited cytotoxicity against human Saos-2 osteosarcoma cells under normoxia or hypoxia. It was found that the relative cytotoxicity on the Saos-2 cells was different in hypoxic versus normoxic conditions [31].

### Genus *Hylocereus*

Pitaya (family Cactaceae, subfamily Cactoideae), commonly known as "dragon fruit", has generated considerable consumer interest because of its attractive color and micronutrient content. White-fleshed pitaya is considered a tropical vine cactus, and it is the most cultivated species in the cactus family. Originating in Central and South America, it is used as an ornamental and fruit crop and named for the wavy margins of its ribs. The stems are scandent, creeping, crawling, or clambering with many branches, joints, and ribs and visible aerial roots. This cactus produces a huge trumpet-like flower and a large colorful fruit with scales resembling those of an artichoke. The solid mass of white flesh inside the red or pink fruit is enlivened by small black seeds, and the fruit is generally thornless. This cactus is easily grown in warm areas, is sensitive to temperatures over 40 °C and below 10 °C, enjoys compost and ample water and grows well on walls, trees, or trellises.


**Fig. 1** Pictures of plants of the Cactaceae family exhibiting anticancer properties: **A** *O. ficus-indica*, **B** *O. humifusa*, **C** *H. ubdatus*, **D** *H. polyrhizus*, **E** *M. geometizans*, **F** *S. thurberi*, **G** *S. stellatus*, and **H** *C. peruvianes* (*C. quadrangularis*). (Color figure available online only.)

*In vitro studies*: One study conducted by Kim et al. [32] investigated the total polyphenol and flavonoid content and antioxidant activity of extracts of the flesh and peel of white-fleshed and red-fleshed pitayas [*Hylocereus undatus* (Haworth) Britton & Rose, **Fig. 1 C** and *Hylocereus polyrhizus* (F. A. C. Weber) Britton & Rose **Fig. 1 D**, respectively] collected from Jeju Island, Korea. Their antiproliferative effect on several cancer cell lines was also investigated. Methanol extracts of the peels of both pitayas showed antiproliferative activity against AGS human gastric and MCF-7 breast cancer cells stronger than exhibited by the flesh extracts. Positive correlation was found between peel and flesh content of polyphenols and flavonoids, and their respective antiproliferative activities. Negative correlations were found between percent cell viability of HeLa, AGS, and MCF-7, and the total polyphenol content. Wu and colleagues [33] showed that the peel of red-fleshed pitaya is a stronger inhibitor of the growth of B16F10 melanoma cancer cells than the flesh. In another study, NO-induced proliferating MCF-7 cells were treated with methanol extracts of cactus fruits. Chiku and "dragon fruit" extracts exhibited remarkable inhibition of cell proliferation. The results were attributed to the scavenging of the cell proliferation-inducing nitric oxide by phytochemicals included in the fruit extract, resulting in the inhibition of MCF-7 cell proliferation [34].

A patent discloses an anticancer pharmaceutical composition containing *H. undatus* extract capable of suppressing cancer cell proliferation and used for the prevention and treatment of cancer [35].

### Genus *Myrtillocactus*

*Myrtillocactus geometrizans* (Mart. ex Pfeiff.) Console (Bilberry cactus, Whortleberry cactus, or Blue Candle, **Fig. 1 E**) is a species of cactus in the genus *Myrtillocactus* native to central and northern Mexico. It is a large, shrubby cactus and can grow to be 4–5 meters in height with candelabra-like branches. The stems are 6 to 12 cm in diameter with five or six ribs. The flowers are white, pale yellow, or cream colored, open in the morning, and

are pollinated by bees and flies. It is a fast growing cactus, tolerant of poor soils and mild frosts and heat up to 45 °C. It does not grow well in saline soil or heavy shade. The fruit is a berry, 1 to 2 cm in diameter, resembling a blueberry.

*In vitro studies*: The sterols peniocerol and macdougallin isolated from *M. geometrizans* showed cytotoxicity against several human cancer cell lines, including PC-3 human prostate carcinoma, K-562 leukemia, U-251 central nervous system carcinoma, MCF-7 breast carcinoma, and HCT-15 colon carcinoma. Peniocerol and macdougallin displayed moderate cytotoxicity against all cancer cell lines with $IC_{50}$ values between 7.55 and 24.73 µM. Peniocerol was more active than macdougallin against all the human cancer lines tested, except K-562 cells, against which macdougallin showed higher activity than peniocerol. The $IC_{50}$ values were found to be an order of magnitude higher than those exhibited by doxorubicin [36].

### Genus *Stenocereus*

*Stenocereus* is a genus of columnar or tree-like cacti. *Stenocereus thurberi* ssp. *littoralis* (K.Brandegee) N.P.Taylor (also called organ pipe cactus, **Fig. 1 F**) is native to Mexico and the southwestern United States. It is found in rocky desert areas. This cactus species has several narrow stems that rise vertically, growing from a single trunk. The stem can be 15 to 20 cm thick and grows to a height of five meters, usually with no branches, giving the plant its nick-name. Mature plants produce funnel-shaped white flowers that open at night and close during the day, usually pink or white in color with reddish sepals. The flowers are pollinated by bats, wild bees, and flies. The fruit is a round, thorn-covered ball, very sweet with numerous black seeds inside the crimson flesh. The plant likes well drained soil and is sensitive to frost, being usually planted as a dry garden fruit or by a southern wall.

*S. thurberi* has profound influences on skin cancers and lesions. Though most of the evidence is anecdotal at this time, this is a line of research worth pursuing. Yetman [37] described the folkloric medicinal uses of the plant: "*the fleshy moist stem is singed to remove spines then applied directly to the flesh for snake and insect bites, a remedy that I tested with positive results when an assassin bug bit my colleague*". The plant is known to be a healing one in Mexico, and it is the market place cure for skin cancers and topical wounds of all kinds.

*In vitro studies*: Seventeen triterpenes isolated from cacti and 10 derivatives thereof were examined for the *in vitro* inhibition of tumor-promoting effects, such as the stimulation of $^{32}Pi$ incorporation into phospholipids of cultured cells. The inhibitory potency of betulinic acid, extracted from *Stenocereus stellatus* (Pfeiff.) Riccob. (**Fig. 1 G**), and that of its acetylated derivative were found to exceed by far those of the other compounds tested (42.2 % and 100 % at a dose of 5 µg/mL and 50 µg/mL, respectively) [38].

### Genus *Cereus*

*Cereus* cacti are large tree-like columnar cacti with four to ten well-defined ribs, thick stems, large white flowers, floral tubes that are sometimes scaly, and tasty pink or red fruits that grow out of the rib margins. They are pollinated by bees, bats, and birds though the flowers are fully open only at night and close two to three hours after sunrise. The plants are able to endure temperatures from − 5 °C to 45 °C and are tolerant of many soil types. They are found in the southwestern United States, Mexico, and Central America. The *Cereus* family includes many species, some of which have been moved into other botanical families as more is learned about columnar cacti.

*Cereus* cacti are described as potential crop plants but are also mentioned as plants used to treat cancer, especially *Cereus quadrangularis* Haw. (**Fig. 1 H**) [39]. The latter is also mentioned by Karimi et al. [40], under its synonym *Cereus peruvianus*, as a medicinal plant effective in treating breast cancer among other diseases.

### Non-specified cacti

*In vitro studies*: The polysaccharides of the cactus cladode consist of rhamnose, fructose, galactose, xylose, arabinose, mannose, and uronic acids, and have been confirmed to possess diverse biological activities, including anticancer efficacy. Guo [41] described the extraction, purification, structure, and bioactivity of polysaccharides from the cactus cladode. The biological effects of the polysaccharides, flavonoids, and alkaloids present were reported, with special emphasis on their role in the prevention and treatment of chronic diseases, including cancer [42].

An invention describes a process for extracting cactus juice and the application thereof in several oncologic diseases, which consists of selecting a cactus with special characteristics, sectioning the arms thereof in a transversal manner for extracting the white color pulp and then cooking the same, the pulp being subjected to a filtration process so as to be subsequently stored in containers and used as a treatment of different diseases [43].

The antitumor effect of wild cactus polysaccharide on *in vitro* cultivated SK-MES-1 lung squamous carcinoma cells was investigated. The lowest inhibition concentration and tumor inhibitive ratio of wild cactus polysaccharide to SK-MES-1 for 24 h and 48 h were 0.0625 mg/mL and 34.06 %, and 0.0625 mg/mL and 35.37 %, respectively [43].

*In vivo studies*: The antitumor effect of polysaccharides extracted from cactus pear fruit in S180 murine sarcoma-bearing mice was investigated. The extracted polysaccharides possess certain antitumor effects, which could induce apoptosis, increase antioxidation and promote immune responses [45].

A study investigated the antitumor effects of three kinds of cactus polysaccharides on mice bearing S180 carcinoma and H22 hepatocellular carcinoma. The results showed that the three polysaccharides have antitumor effects on S180 carcinoma and also a life lengthening effect on H22 hepatocellular carcinoma-bearing mice [46]. Another study showed that the cactus polysaccharides increased the content of RBC-CaR and RFER, decreased the content of RFIR and raised the sialic acid content. The cactus polysaccharides further improved the erythrocyte function of tumor-bearing mice, which was assumed to be one of the antitumor mechanisms [47]. Polysaccharides of a cactus increased microviscosity and decreased membrane lipid fluidity of the S180 cell membrane, leading to the conclusion that the polysaccharides of a cactus change the function of tumor cell signal transduction and communication to play a key role in antitumor effects [48].

## Conclusion and Perspective

The gradually emerging trend of applying bioactive extracts and pure components of plant origin to treat and prevent cancer stems mainly from the almost unavoidable severe side effects involving the use of chemical drugs and their frequently low efficacy. The experimental works disclosed in this review indicate

the value of plants of the Cactaceae family as potential sources for preventive and curative anticancer drugs.

Based on available literature as presented in our manuscript, studies conducted using various cancer cell lines have provided impressive evidence of anticancer activities. Only a limited number of studies have documented similar results using *in vivo* tumor models. Currently, very limited information is available on whether concentrations showing activity *in vitro* are reachable in the blood or serum of laboratory animals or not. As a matter of fact, the same plant or bioactive component has not been studied in both *in vitro* and *in vivo* systems. While this represents a limitation to our existing knowledge on the anticancer potential of plants belonging to the Cactaceae family, it is expected that future studies will explore this area of research.

As this review shows, only a few plants out of the 1500 included in this family have been tested for their chemopreventive and anticancer effects, while the great bulk still remains unexplored. Also a very small number of pure components isolated from cacti were tested for their antineoplastic properties. In most cases, only crude extracts or crude pressed juices were tested either *in vitro* or *in vivo*. Somewhat more refined extraction procedures are mentioned only twice [18,27]. Only one publication compares the anticancer activity of a crude extract derived from a cactus to that of a pure component isolated from it [28]. No mention is made of highly bioactive extract combinations or of clinical trials. Also, no mention was found of actual or possible side effects involving the use of these plants in cancer prevention and cancer therapy. We are in the opinion that the importance of this review resides in directing attention of the scientific community to this family of plants, which is on the one hand, highly potential in treating and preventing cancer, but on the other hand still almost unexplored.

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## Conflict of Interest

The authors have no conflicts of interest.

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