Chapter 23
Anticancer Activity of *Opuntia* spp.

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Abstract According to the World Health Organization (WHO), cancer was ranked as the second leading cause of death. Research on natural products has recently received a lot of attention from health professionals for improving overall well-being and the prevention of diseases, including cancer. Many herbs have been screened for anticancer activity *in vitro* and *in vivo* as an alternative drug or in combination with chemotherapy. *Opuntia* spp. (prickly pear cactus) which belongs to the Cactaceae family is a xerophytic plant with 200–300 species. It is distributed worldwide and has great economic potential. *Opuntia* spp. fruits revealed to be

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promising natural sources for the production of functional products and the development of novel chemotherapeutic agents. Studies have demonstrated the cytotoxic effects of various parts of *Opuntia* (fruits), with or without peels and seeds, the cladodes or stems, and even the roots, on cancerous cell lines. The cactus pear fruit extract inhibits the proliferation of cervical, ovarian, and bladder cancer cell lines *in vitro*, and suppresses tumor growth in the nude mice ovarian cancer model *in vivo*. It was reported that the anticancer activity is mostly because of bioactive polysaccharides that induce cell apoptosis or cell cycle arrest and angiogenesis suppression with minor toxicity on normal cells. This chapter aims to study the anticancer activity of *Opuntia* spp.

Keywords Cactaceae · Prickly pear · Polysaccharides · Antitumor · Antiproliferative

Abbreviations

ADP Poly (ADP) ribose polymerase
DNA Deoxyribonucleic acid
O. *Opuntia*
PARP Ribose polymerase
ROS Reactive oxygen species
WHO The World Health Organization

1 *Opuntia* spp. Derived Products as Antiproliferative Agents in Human Colon Cancer Cell Line (HT29)

Cancer is a devastating disease and treatments for recurrent and metastatic diseases remain a center of clinical attention. A potential solution to this problem lies in using plant-derived compounds or phytochemicals, which are considered pharmacologically safe and may provide a viable option for anticancer therapy. While continuing efforts have been made for discovering new molecular target-based molecules, there is an emerging interest in the chemotherapeutic application of natural substances.

Opuntia spp. have been characterized extensively at the biochemical level, and their biological effects, including therapeutic properties against cancer. Many studies have shown that the cactus has antiproliferative activity against a wide range of cancers (Garcia-Solis et al., 2009; Feugang et al., 2010). Kim et al. (2014) showed that extracts from *O. humifusa* cladodes induced apoptosis in MCF-7 cells and human colon SW-480 cells. The polyphenol-rich juice concentrates of *Opuntia ficus-indica* and *Opuntia robusta* inhibited cancer (human colon carcinoma HT29

cell line) cell growth and induced cell cycle arrest in different checkpoints G1, G2/M, and S, but not to Caco2 (Serra et al., 2013). Natural extracts from juice residues (peels and seeds) were reported to be more effective than juice concentrates on inducing a cell-cycle arrest in the same cells. Interestingly, this effect paralleled an increase of reactive oxygen species (ROS) in the cells, which suggests a ROS-induced cell death probably due to the extracts' pro-oxidant effects. The presence of compounds such as β-cyanines, flavonoids, and phenolic acids could be responsible for cell cycle arrest.

Antunes-Ricardo et al. (2014) evaluated the cytotoxic effects of *O. ficus-indica* cladode extracts of purified isorhamnetin glycosides on two models of human colon cancer cell lines (HT-29 and Caco2), representing apoptosis-resistant and apoptosis-susceptible cell lines, respectively, while normal fibroblasts (NIH 3 T3) were used as control. Authors reported that cladode extracts and isorhamnetin glycosides were more cytotoxic to HT-29 cells than to Caco2 or to control, with an effect of the glycosylation pattern.

The effect of *O. ficus-indica* fruit aqueous extract and its betalain pigment indicaxanthin on the proliferation of the human colon cancer cell line Caco2 was studied (Naselli et al., 2014). The authors revealed a dose-dependent apoptotic effect on proliferating cells, while no effect was reported on differentiated cells. In this study, indicaxanthin presented an epigenomic consequence on the tumor suppressor gene p16INK4a, through demethylation of its promoter and stimulation of its expression.

2 Anticancer Properties of *Opuntia humifusa* Extracts Against Human Cervical Carcinoma Cells

The uterine cervix's carcinoma is the second most common women cancer in developing countries (Alvarez-Salas et al., 2007). Current treatment, radiotherapy, and adjuvant chemotherapy have limited efficacy. A potential solution to this problem lies in using plant-derived compounds that are considered pharmacologically safe and may provide a viable option for anticancer therapy. The water extracts from *O. humifusa* have been reported to exert anticancer effects on human glioblastoma or astrocytoma, epithelial-like (U87MG) cells (Hahm et al., 2010). One strategy for cancer control is chemoprevention, which uses dietary or synthetic agents to prevent or to slow carcinogenesis. In another study, *Opuntia humifusa* extracts (Hahm et al., 2010) evaluated the inhibition of growth of U87MG human glioblastoma cells. The results showed that aqueous fractions from *O. humifusa* induce G1 arrest and non-apoptotic cell death and significant increase in ROS production in U87MG cells inhibiting U87MG human glioblastoma cell proliferation.

Cactus fruit ethyl acetate extracts containing flavonoids, *trans* taxifolin, and dihydrokaempferol also suppressed HeLa cervical carcinoma cell proliferation (at ≥100μg/mL concentrations). Simultaneously, normal human BJ fibroblasts were unaffected, suggesting potential application as an intervention for human cervical

carcinoma management. The anticancer effect of *Opuntia* fruit extracts has also been reported *in vitro* using ovarian, cervical, and bladder cancer cells and *in vivo* using a nude mice ovarian cancer model.

2.1 Growth Inhibitory Effect of Cactus Pear Solution on Human Ovarian Cell Lines

Results show that the cactus pear inhibited the growth of different cancer cells *in vitro* and in *vivo*. Cactus products inhibited cancer cell growth with concentrations as low as 5%. The cell cycle was also affected at this concentration with an increase in the G1 phase.

2.2 Extracts of O. humifusa *Inhibit Cell Proliferation in Human Cervical Cancer Cells*

HeLa cells were treated with the extracts for 24 h at concentrations ranging from 100 to 1000 lg/mL, and the number of viable cells was determined using the MTT-based assay. Hexane extracts of *O. humifusa* significantly suppressed cell proliferation. Additionally, treatment with the ethyl acetate extracts (100 lg/mL) of the fruit, stem, and root significantly decreased the proliferation of HeLa cells. The effects of *O. humifusa* extracts on cell growth were further examined using BJ cells. Treatment of the cells with the ethyl acetate extracts markedly increased the number of viable cells.

3 Anticancer Properties of *Opuntia ficus-indica* Induces Apoptosis in Human Chronic Myeloid Leukemia Cell Line-K562

Betalains are water-soluble nitrogen-containing pigments that are responsible for the bright red or yellow color of fruits. One of these plants, *Opuntia ficus-indica* (L.) Mill. (cactus or prickly pear) contains betalains in the fruits (Stintzing et al., 2003). Betalains are associated with some beneficial health effects, including anticancer activity. Besides, a role for betalain pigments in the chemoprevention against lung and skin cancers has been documented (Kapadia et al., 1996). It is demonstrated that natural food colors, such as betanin, can inhibit the cell proliferation of various human tumor cells (Muntha Reddy et al., 2005). In a previous work, Sreekanth et al. (2007) reported that betanin isolated from the *Opuntia ficus-indica* fruits showed antiproliferative activity on human chronic myeloid leukemia cell line (K562)

through the intrinsic apoptotic pathway, and cell death was recorded at an inhibitory concentration (IC_{50}) of 40 mM betanin. In particular, this compound induced cell cycle arrest in the sub G0/G1 phase and promoted apoptosis in leukemia cells.

Further studies involving scanning and transmission electron microscopy revealed apoptotic characteristics such as chromatin condensation, cell shrinkage, and membrane blebbing. Agarose electrophoresis of genomic DNA of cells treated with betanin showed fragmentation pattern typical for apoptotic cells. Flow cytometric analysis of cells treated with 40 mM betanin showed 28% of cells in the sub G0/G1 phase. Betanin treatment to the cells also induced the release of cytochrome c into the cytosol, poly (ADP) ribose polymerase (PARP) cleavage, down-regulation Bcl-2, and reduction in the membrane potentials. Confocal microscopic studies on the cells treated with betanin suggest the entry of betanin into the cells. Thus, these studies demonstrated that betanin induces apoptosis in K562 cells through the intrinsic pathway and is mediated by the release of cytochrome c from mitochondria into the cytosol and PARP cleavage. The antiproliferative effects of betanin add further value to the nutritional characteristics of *O. ficus-indica*.

4 Anticancer Activity of *Opuntia* Extract on Human Breast Cancer Cell Line

Cancer is one of the leading causes of death worldwide. In particular, breast cancer is one of the more frequent causes of premature mortality in the female population. Cancer stem cells have gained attention in the last years as responsible for tumor progression and resistance to therapy in breast cancer tumors (Ferrari et al., 2013). At the moment, chemotherapy seems to be the only possible treatment involving side effects. Therefore, great efforts are devoted to developing new strategies using therapeutic agents to improve and optimize the treatment (De la Mare et al., 2014). The result has been reported that the ethyl acetate extract of *O. humifusa* stem repressed breast cancer cell proliferation (Kim et al., 2013). *Opuntia polyacantha* alkaloid extract shows great cytotoxic activity against MCF-7 cells compared with its minor cytotoxic effect on the normal cell line, which may open an innovative study in cancer treatment as either an alternative drug or immunoadjuvant agent, especially its safety (Lubna Abdulazeem et al., 2018).

5 Anticancer effect of Prickly Pear (*Opuntia ficus indica*) Juices

It appears that *Opuntia ficus-indica* has been subject to intensive exploitation due to its great compositional diversity. Several studies have agreed that *Opuntia ficus indica* juice was rich in minerals and vitamins (Moßhammer et al., 2006; El-Gharras

et al. 2006) and may potentially be included in animal and human diets. It could be noted that the cactus fruit juice of *Opuntia ficus indica* is rich in betalains (betanin and indicaxanthin) (El-Gharras et al., 2008), and also elevated in polyphenolic flavonoids (quercetin, kaempferol, and isorhamnetin) and various carotenoids. These fruits have shown several effects, such as anticancer (Zou et al., 2005). The *in vitro* cytotoxicity was measured toward the P-815 cell line by the growth inhibition assay determined by the MTT viability assay. It was found that the juice of different cultivars exerts a dose-dependent growth inhibition against the P-815 cell line.

6 Anticancer Effects of Prickly Pear (*Opuntia ficus indica*) Seeds Oil

The prickly pear seed oil composition and its chemical characteristics were investigated (Salvo et al., 2002). Ramadan and Morsel (2003) compared the seed and pulp oil composition. All the authors have agreed that *Opuntia ficus-indica* seed oil is rich in polyunsaturated fatty acids (PUFA) and vitamins and may be included in animal and human diets. However, data on the nutritional value of prickly pear oil are at present unknown. This oil also had an inhibitory effect on the growth of two different types of cancer cells [Colo-205 cell line and Hepatocellular carcinoma cell line (HepG2)]. The findings of this trial highlighted the beneficial effect of *O. ficus-indica* seed oil on health.

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