Review
ISSN 2413-0516

# *Opuntia ficus-indica* and its Potential Effects on Cancer

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*(Submitted: 22 August 2023 – Revised version received: 07 September 2023 – Accepted: 21 September 2023 – Published Online: 29 October 2023)*

**Abstract**
Cancer is the second leading cause of death worldwide, with an estimated 19.3 million new cases and 10.0 million deaths in 2021. Genetic and environmental factors, including nutrition, play an important role in cancer development. At present, health professionals and the public have become highly interested in natural products and healthy food for preventing or treating cancer. Several natural products, such as fruits and vegetables, have demonstrated anticancer effects. *Opuntia ficus-indica* (OFI), commonly known as prickly pear or cactus pear, is a plant that has numerous beneficial properties. It serves as a source of dietary fibres, vitamins and various bioactive compounds with diverse health benefits. These compounds are associated with anti-inflammatory, antioxidant, antimicrobial, hypoglycaemic and neuroprotective properties. Different parts of the plant, including the fruit pulp and peel, cladodes (pads) and seeds, have been scientifically studied, and they have demonstrated therapeutic potential while being considered safe for human consumption. However, there is limited awareness and scientific information about OFI as a fruit. Reviewing existing knowledge and research on it is necessary to shed light on its potential anticancer properties. By consolidating the available information on OFI, we can gain a better understanding of this fruit and its potential role in cancer prevention and treatment.
**Keywords:** Cancer, OFI, prickly pear, anticancer, chemoprevention, antioxidants

## Introduction

Cancer is a group of deadly diseases. The incidence of cancer continues to increase worldwide, with approximately two in every five people developing cancer in their lifetimes. In many countries, cancer is the second most common cause of death after cardiovascular disease, accounting for nearly 10 million deaths in 2020. In 2018, approximately 9.6 million people died due to this disease.[1] Cancer is likely to be considered preventable. Cancer risk can be reduced in two ways: avoiding cancer-causing biologic, chemical and physical agents and modifying dietary habits by increasing the consumption of fruit and vegetables. A healthy diet, regular physical activity and maintenance of the optimum body weight prevent approximately 30%–40% of cancer incidents, while modifying the diet alone by increasing vegetable and fruit intake may help prevent approximately 200,000 cancer-related deaths annually.[2]

The clinical management of cancer is challenging because of recurrence or metastasis. The treatment options depend on tumour type, histological grade and stage of the tumour. Despite recent developments in local and systemic treatment methods, conventional treatments, such as chemotherapy and radiation therapy, remain commonly used to treat various types of cancers. However, these therapies have limitations because of the development of therapy-induced innate and/or acquired tumour resistance or local/systemic toxicities that cause either reduced response, nonresponsiveness or tumour relapse after an initial anti-tumour response. A potential solution to this problem is preventing cancer development by changing one's lifestyle, such as adopting dietary modifications, along with taking the right nutritional supplements or using plant-derived compounds or phytochemicals with anticancer properties, which can enhance the effectiveness of chemotherapy or radiation therapy and are considered pharmacologically safe and low in toxicity. Antioxidants, dietary supplements, fruits, vegetables and other dietary elements (phytochemicals and minerals) are being investigated for their actions in cancer prevention. At present, nutraceuticals have drawn research attention, and there has been much effort towards the development of natural compounds that prevent or treat many cancers.

Cancer undergoes three stages: initiation, promotion and progression. The initiation stage starts when a normal cell is exposed to a carcinogenic substance and becomes a cancer cell. Tumour promotion is a prolonged process that provides the conditions for clonal expansion and genetic instability of preneoplastic and premalignant cells. The development of a tumour with the ability to invade adjacent tissues and metastasise to another part of the body is considered progression, which is the last stage in cancer development. To prevent cancer development, artificial, organic or biological chemicals are used in a process known as chemoprevention. Two types of chemopreventive agents are used: blocking agents and suppressing agents. Blocking agents prevent carcinogens from entering the target area, whereas suppressing agents prevent initiated cells from transforming into malignant cells at either the promotion or progression stage. The initiation and promotion stages can be prevented or reversed by chemopreventive therapy. Moreover, the transformation of precancerous cells into cancerous ones can be slowed down or completely stopped. Chemoprevention can involve the use of natural or synthetic agents.[3,4]

### *Why Natural Compounds?*

Chemoprevention studies started in the 1920s[5] but were suspended until the reports by Sporn et al. in the 1970s. They showed that natural vitamin A had excessive toxicity and inadequate biodistribution and had been replaced by its synthetic analogue (retinoids).[6] In clinical trial I, vitamin A with 13-cis-retinoic acid (13-cRa) decreased the size of oral premalignant lesions and reversed dysplasia.[7] In clinical trial III, patients with leukoplakia were treated with high-dose isotretinoin for three months, followed by either beta carotene (30 mg per day) or low-dose isotretinoin. The results showed that high-dose induction therapy followed by low-dose

isotretinoin therapy was significantly more effective against leukoplakia than beta carotene therapy alone, and it was also easily tolerated.[8] In clinical trial III, daily treatment with high doses of 13-cRA therapy showed a decreased incidence of second primary tumour (SPT) in patients who have been treated for squamous cell carcinoma of the head and neck cancer, and provided protection lasting for two to three years.[9,10] The novel biologic agent combination of IFN-α, 13-cRA and α-tocopherol was evaluated in clinical trial II, and the results showed that this combination was effective in delaying SPT.[11] Phase III, which aims to study this combination (vs. no treatment), has been started but is currently delayed because of patient accrual issues.

The discovery of biomarkers, such as epidermal growth factor receptors (EGFRs), cyclo-oxygenase-2 (COX 2) and Ras, which are linked to disease progression, and efforts to develop novel targeted inhibitors for these biomarkers have created new possibilities for chemoprevention. Several drugs have been developed, including celecoxib and rofecoxib as COX 2 inhibitors, erlotinib and gefitinib as EGFR inhibitors, and farnesyltransferase inhibitors.[12-15] However, because of the lack of long-term safety data in patients without cancer, two clinical trials investigating the use of gefitinib and tipifarnib in reversing lung lesions have been terminated.

Safety is always a priority when conducting studies involving human participants, especially those without any signs of obvious cancer. An ideal preventive treatment should be safe, effective at low doses, reasonably priced and purchasable. However, patients' participation in chemoprevention trials can sometimes be challenging because of the toxicity of the drugs being investigated. Nowadays, nutraceuticals have drawn the attention of researchers and the general public for their potential to suppress and reduce the risk of cancer.[16-19] Epidemiological in vivo and vitro studies have demonstrated the relationship between vegetable and fruit consumption and the risk of cancer; they found that greater vegetable and fruit consumption was associated with a protective effect against cancers of the stomach,[20] oesophagus,[21] lung,[22] oral cavity and pharynx,[23] endometrium,[24] ovary,[25] prostate,[26] bladder,[27] kidney,[28] liver,[29] pancreas[30] and colon.[31,32] The types of vegetables or fruits that show the most protective effects against cancer are raw vegetables, green leafy vegetables, allium vegetables, carrots, cruciferous vegetables, tomatoes, green tea, ginger, soybeans, citrus fruits and berries. Carotenoids, flavonoids, isothiocyanates, dithiolthiones, indole-3-carbinol (I3C), phytoestrogens (genistein and daidzein), allium compounds, phytosterols, inositol hexaphosphate, saponins, dietary fibre, folate, omega 3, D-limonene and vitamins C and E are the most common substances present in vegetables and fruits that may help protect against cancer.[33]

Despite the existence of much evidence regarding the role of natural products in preventing cancer, clinical trials have only recently begun to examine these products. Several compounds are being studied in clinical trials for cancer chemoprevention, including curcumin (in turmeric), genistein (from soybeans), pomegranate extract, omega-3 fatty acid (from walnuts and vegetable oils), lycopene (from tomatoes), I3C (from broccoli), sulforaphane (from asparagus) and resveratrol (from grapes and peanuts).[2,34] Natural products have great potential for cancer prevention because of their safety, low cost and oral bioavailability. In this review, we discuss the potential of *Opuntia ficus-indica* (OFI) in cancer prevention in vitro and in vivo.

## Methods

This review article summarises the potential of OFI in cancer prevention in vitro and in vivo. The literature review used several databases, such as Google Scholar, PubMed and Science Direct. The investigation was completed on August 1, 2023. Many terms were utilised, including OFI and cancer, prickly pear and cancer prevention, natural products and cancers. We did not impose a time restriction despite supporting more current investigations. Comparable articles were discovered by looking through the references of pertinent articles.

### *General Information on Opuntia ficus-indica*

This review attempts to provide an overview of OFI and its antioxidant and anticancer activities. *Opuntia ficus-indica* is the scientific name for the most widely consumed species of *Opuntia*, belonging to the cactus family (*Cactaceae*). The *Cactaceae* family comprises 130 genera and 1,500 species.[35] *Opuntia* is commonly known as prickly pear. Its other common names are *Indian fig, Barbary fig, cactus pear, paddle cactus, sabra, nopal* (in Mexico), *higo chumbo* and *chumbera* (in Spain) and *tuna* (in Spain and Latin America); locally, it is called *barshomi* or *teen shawky* (Figure 1).[36] The different names for *Opuntia* reflect its wide range of uses and cultural significance. This plant grows in tropical or subtropical areas

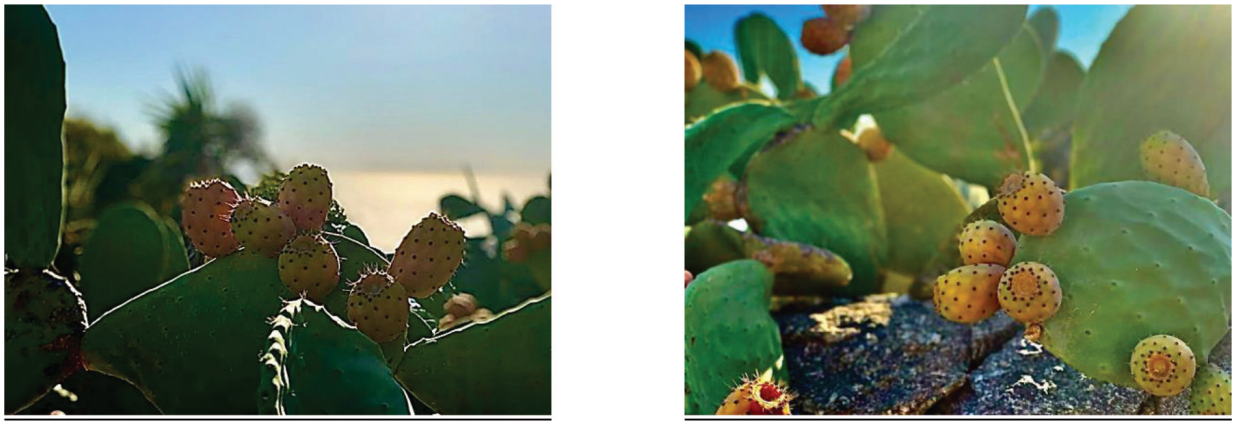

Fig. 1 **OFI (prickly pear).**

in Mexico, Latin America, Africa and Mediterranean countries. It is found wild in arid and semiarid plateau regions and is now grown in many parts of the world. *Opuntia ficus-indica* fruit is produced in the summer over a very short period. Its fresh fruits do not last too long, even when stored in refrigerated conditions.[37]

The prickly pear cactus has four parts: the root, the vegetative part, the fruit and the flower. The vegetative part, which comprises flattened stems, is known as nopale, pads, joints or cladodes. The main function of the vegetative part is photosynthetic. The cactus pear fruit has a cylindrical shape, and the outer shell of the fruit contains a few thorns. The cactus pear presents in several colours, such as white, green, yellow, orange, red, purple and even brown. In general, cladodes are rich in pectin, mucilage and minerals, whereas the fruits are good sources of vitamins, amino acids and betalains.[38] The fruit of *Opuntia* is edible and a popular ingredient in many dishes, especially in Mexico. The pads of *Opuntia* can also be eaten cooked or as salad and are good sources of fibre, carbohydrates and vitamins. The fruits and pads are used to create several products, including jam, wine, pickle, body lotions, shampoo and creams.[39]

*Opuntia ficus-indica* fruits and pads are used for medicinal purposes to treat several diseases, given their pharmacological activities, including anti-ulcer, antimicrobial, antiviral, anti-inflammatory, anticancer, antioxidant, antidiabetic, antiobesity, antihypertensive, neuroprotective and hepatoprotective effects.[40] *Opuntia ficus-indica* is an excellent candidate as a superfood because it contains important components, such as carotenoids, polyphenolic compounds, betalains and flavonoids (isorhamnetin, kaempferol and indicaxanthin [Ind]). It is also a rich source of vitamins C, E, A, B1 and B2, as well as minerals, such as calcium, potassium, magnesium, iron and phosphorus. It constitutes amino acids, carbohydrates, fibres and protein. Although Native Americans knew about the benefits of this fruit in treating many diseases, such as diabetes, high cholesterol, inflammation and infections, these were not known by the rest of the world because studies on the biological functions of cactus (*Opuntia*) started only in the 1980s.[38] Recently, food, nutritional and even pharmacological science has given more attention to the chemical components and nutritional value of *Opuntia* spp.

## Antioxidant Activity

Oxidation reactions can occur when a material transfers electrons or hydrogen to an oxidising agent. These reactions can generate free radicals, which are highly reactive species because of the presence of unpaired electrons. Free radicals can cause oxidative damage to various biological molecules, including lipids, proteins and DNA.[41] Oxidation is not the only cause of cancer; inflammation is another factor in carcinogenesis. Inflammation causes cancer via several mechanisms, including the production of free radicals by inflammatory cells. Antioxidative action is one of many mechanisms by which fruit and vegetable substances might exert beneficial health effects. Several foods, especially those with vegetable and fruit origins, contain reducing substances known as antioxidants, which can neutralise free radicals, preventing them from causing damage and acting as chemoprotective agents.[42] Compounds with antioxidant activity (AA) could play important roles in the prevention of many health problems, such as carcinogenesis, metabolic events, immune disorders and neurodegenerative diseases.

*Opuntia ficus-indica* has been proposed to have interesting AA and protective effects because of the presence of antioxidants, such as carotenoids, flavonoids, ascorbic acid, betalains, polyphenols and vitamins E and C.[43,44] Chavez-Santoscoy et al. showed that prickly pear juices (PPJs) have greater antioxidant capacity than strawberry, plum, orange, grapefruit, red and white grapes, kiwi, apple, pear and tomato.[45] Petruk et al. evaluated the antioxidant capacity of OFI cladodes by treating keratinocytes with the extract from cladodes and then exposing the cells to Ultraviolet A (UVA) radiation. They found that cladode extract protected against UVA-induced oxidative stress in normal human keratinocytes.[46] Furthermore, the AA of nopal was compared with that of different foods, and the results showed that nopal had a greater AA than coffee and garlic, and a lower AA than plum and chia seeds.[47] A recent study demonstrated that the antioxidant properties of prickly pear cladodes were higher in dry mass than in fresh mass and that the concentration of antioxidants was higher in the third and fourth stages of development.[48]

The phenolic composition and AAs of OFI peel and flower were tested, and the results showed that both OFI peel and flower teas exhibited high AAs measured by several tests (1,1-diphenyl-2-picrylhydrazyl radical assay, reducing power and hydrogen peroxide scavenging activity).[49] In addition, studies have shown that the antioxidant capacity in the peel was higher than that in the seeds and that fruits with light-green or yellow-brown peel had higher antiradical activities than those with red-purple peel.[50]

The AA of OFI was also examined in vitro using three methods: traditional antioxidant (oxygen radical absorbance capacity [ORAC] and Trolox-equivalent antioxidant capacity [TEAC]) and lipoxygenase-fluorescein (LOX-FL) methods. The LOX-FL results showed the highest antioxidant capacity correlated with betanin content.[51] Betalains are water-soluble pigments. Prickly pears contain two betalainic derivatives, betacyanin (red colour) and betaxanthine (yellow-orange colour), which have beneficial effects in the redox-regulated pathways implicated in cellular growth and inflammation; no toxic effects have been observed in humans.[52] Albano et al. evaluated betacyanin (betanin), total phenolics, vitamin C and antioxidant capacity using two methods: TEAC and ORAC assays in two differently coloured OFI fruits—a purple fruit and an orange fruit. They found that purple cactus pears contain higher betanin, phenolics, vitamin C and antioxidant capacity than orange cactus pears.[53] Kuti et al. also examined the antioxidant compounds in extracts from four (*Opuntia* species) fruit varieties (green, purple, red and yellow skinned), and the results showed that purple-skinned fruit extracts had a stronger AA than other varieties.[44]

The most active organ for oxidation in the human body is the liver. The liver is responsible for breaking down and metabolising a variety of substances, including fatty acids, carbohydrates and proteins. In this process, oxygen is used to oxidise such substances, releasing energy and producing free radicals. Recently, the hepatoprotective role of the OFI plant has been studied, and several investigations and symposia have been initiated, which have in turn increased publications, books and book chapters on this topic.

Ncibi et al. studied the role of OFI cladode extract against liver damage induced in male Swiss mice by an organophosphorus insecticide, chlorpyrifos (CPF); the results showed that CPF is hepatotoxic and that OFI stem extract protects the liver and decreases the toxicity induced by this organophosphorus pesticide.[54] Moreover, Bacha and his group conducted studies to investigate the hepatoprotective effects of cactus cladode extract (CCE) against two compounds with hepatocarcinogenic properties: benzo(a)pyrene (BAP) and aflatoxin B1 (AFB1). Their results showed that these two compounds induced significant alterations in oxidative stress markers, such as malondialdehyde and catalase activity; increased the expression of the heat shock proteins Hsp70 and Hsp27 and anti-apoptotic protein BCL-2; and decreased the expression of Bax. Moreover, they induced DNA fragmentation in the liver and chromosomal aberrations in bone morrow cells. The authors found that treatment with CCE prior to or after treatment with BAP and AFB1 reduced the oxidative damage induced in all the markers tested, and showed an antigenotoxic effect by preventing chromosomal aberrations and DNA fragmentation by both compounds. The authors also observed that CCE inhibited the toxic effects of both toxins by differential modulation of the expression of p53, which was increased, and its associated genes, such as Bax and BCL-2.[55,56] According to these results, CCE is considered to have protective effects against carcinogens and to have hepatoprotective capacity.

Reactive oxygen species (ROS) are free radicals generated from the ethanol metabolism process, and they induce oxidative stress in hepatocytes, leading to liver damage.[57] Finding new substances that prevent ethanol-induced liver toxicity and possess hepatoprotective effects is the best strategy to prevent the progression of alcoholic liver impairment.[58] Wiese et al. reported that an extract of OFI could reduce the symptoms of hangovers after consuming alcohol in excess by reducing nausea, dry mouth and anorexia.[59]

The potential effects of OFI PPJs on ethanol-induced liver injury in rats were investigated by Alimi et al. In this study, Wistar rats were chronically administered ethanol at a dose of 3 g/kg body weight for 90 days. This ethanol administration resulted in significant increases in liver lipid and protein oxidation, as well as reductions in glutathione content and the activities of liver antioxidant enzymes, such as superoxide dismutase, catalase and glutathione peroxidase. Additionally, ethanol administration led to elevated levels of liver injury biochemical markers, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, cholesterol and triglycerides. Histopathological examinations also revealed severe liver injuries. However, the pre-treatment of ethanol-fed rats with PPJs at doses of 20 and 40 ml/kg body weight, administered orally, showed interesting results. The administration of PPJs effectively reduced liver lipid and protein oxidation, mitigated histopathological lesions and inhibited alterations in antioxidant enzyme activities. Furthermore, PPJ administration prevented the release of biochemical markers associated with liver injury. The hepatoprotective effects of PPJs may be attributed to their ability to interrupt free radical chain reactions or enhance the activities of endogenous antioxidants.[60] Moreover, Kim et al. isolated six lignan compounds from OFI seeds and tested them against ethanol-treated primary rat hepatocytes; they found that furofuran lignans 4–6 significantly protected rat hepatocytes against ethanol-induced oxidative stress by reducing intracellular ROS levels, preserving antioxidative defence enzyme activities and maintaining glutathione content.[61]

## Anticancer Activity

Medicinal plants can contain various active constituents that contribute to their beneficial effects. These active constituents can be found in different parts of the plant, such as the flowers, fruits with or without peels, seeds, roots, cladodes or stems, or even the entire plant. The active constituents can be present in plant materials in their natural or crude state, or they can be processed or extracted to isolate specific compounds or enhance their bioavailability. Studies have shown that various parts of *Opuntia* exhibit cytotoxic effects on cancer cell lines. However, the choice of extraction solvents and processing procedures can have a significant impact on the biological activity, yield and phenolic component profile of the extracts being studied. Different solvents and extraction techniques can extract different bioactive compounds from plant materials, leading to variations in their overall composition and potential effects.[62]

Shimaa et al. investigated the content of total polyphenols (TPCs) and flavonoids (TFCs) in different extracts of OFI peel. Specifically, the cyclohexanone extract (OFICE), 70% ethanol in water extract (OFI70EE) and 100% ethanol extract (OFI100EE) were analysed, and significant differences in the TPCs and TFCs were observed among the extracts. The OFICE extract exhibited a higher AA than the other extracts. The bioassay using MCF-7 cells demonstrated that the OFI extracts significantly reduced the viability of cancer cells at a concentration of 400 µg/mL after 72 hr of incubation. This suggests that the extracts have cytotoxic effects on MCF-7 breast cancer cells.[63]

The bioactive compounds found in OFI, such as polyphenols, flavonoids and betalains, have been associated with antiproliferative effects and the ability to induce apoptosis. Researchers evaluated the antiproliferative effects of betanin, a principal betacyanin pigment found in the fruits of OFI, on a human chronic myeloid leukaemia cell line called K562. The results demonstrated a dose- and time-dependent decrease in the proliferation of K562 cells when treated with betanin. Further investigations using scanning and transmission electron microscopy revealed apoptotic characteristics in the treated cells, including chromatin condensation, cell shrinkage and membrane blebbing. Agarose electrophoresis of the genomic DNA from betanin-treated cells displayed a fragmentation pattern typical of apoptotic cells. Flow cytometric analysis showed that 28.4% of the cells treated with 40 microM betanin were in the sub G0/G1 phase, indicating apoptosis. Betanin treatment also led to the release of cytochrome c from the mitochondria into the cytosol, the cleavage of poly ribose polymerase, the downregulation of BCL-2 and the reduction in mitochondrial membrane potential. Overall, the findings from this study demonstrate that betanin induced apoptosis in K562 cells through the intrinsic pathway.[64] Moreover, the role of isorhamnetin and its different glycosides, which are the most abundant flavonoids present in OFI, has been demonstrated to induce apoptosis in metastatic human colon cancer cells (HT-29) by inducing mitochondrial damage and an increase in ROS levels.[65]

Opuntiol is a novel bioactive flavonol from the cactus pad of OFI. Opuntiol has recently gained attention for its potential antiproliferative activity. Isolated opuntiol significantly inhibited KB oral carcinoma cell proliferation; it significantly increased ROS generation, caused alterations in mitochondrial membrane potential (MMP) and induced apoptosis in KB cells.[66] Another study showed that opuntiol inhibited the growth of human glioblastoma multiforme cell line U87 and induced apoptosis in these cells by upregulating the expression of active caspase 3.[67]

The anticancer properties of OFI seed oil have also been studied. In vitro studies showed that OFI oil showed weak inhibitory activity against the A-2780 ovarian carcinoma cell line. However, it exhibited significant inhibitory activity against the PC-3 prostate carcinoma cell line.[68] Another study compared the anticancer activity of spiny and thornless OFI seed oils, and the results demonstrated that thornless OFI seed oil might have a higher anticancer effect on primary colon adenocarcinoma cell lines than spiny. This effect is likely mediated by the induction of apoptosis.[69]

The anticancer effects of OFI fruit extracts were tested in vitro and in vivo. *Opuntia ficus-indica* fruit extracts increased apoptosis and growth inhibition in both immortalised epithelial cells and cancer cells (cervical, ovarian and bladder cancer cell lines) in a dose- and time-dependent manner. In vivo experiments showed that animals' body weights did not change with the intraperitoneal administration of OFI fruit extract solution, which indicated that OFI fruit extract is safe and has no significant toxic effects on animals. It also suppressed tumour growth in a nude mouse ovarian cancer model.[70]

In another study, the researchers investigated the in vitro anticancer activity of ethanolic extracts obtained from OFI fruit. The extracts were tested on three different cancer cell lines: A549, H522 and H460. The IC50 values were determined to be 40.00 µg/mL for A549 cells, 42.77 µg/mL for H522 cells and 45.88 µg/mL for H460 cells. Further investigation showed that the active components isolated from the OFI extracts decreased the IC50 values to 15 µg/mL. This suggests that the isolated active components have enhanced anticancer activity compared to the whole extract. The plant extracts were fractionated using column chromatography, resulting in the isolation of five fractions: OFI1 to OFI5. Among these fractions, OFI3 exhibited higher activity in the in vitro anticancer evaluation. In addition to the in vitro studies, an in vivo study was conducted using the OFI3 fraction to evaluate its anticancer activity. The study utilised solid tumour and ascites tumour models using DLA cell lines. The plant fractions also exhibited significant anticancer activity in these models. *Opuntia ficus-indica* at a dose of 200 mg/kg demonstrated 55% inhibition of tumour growth, whereas the standard drug cisplatin (CCDP) resulted in 95% inhibition. Histopathological studies revealed the presence of fibrous cells and the absence of necrosis, inflammatory changes and blood vessels in the high-dose treatment group. These findings indicate the efficacy of OFI as an anticancer agent.[71]

Allegra et al. investigated the effects of Ind, a novel and bioavailable phytochemical found in OFI fruits, against human melanoma, both in vitro and in vivo. The study design involved evaluating the effects of Ind on the proliferation of the A375 human melanoma cell line and in a mice model of cutaneous melanoma. The results demonstrated that Ind effectively inhibited the proliferation of highly metastatic and invasive A375 cells by inhibiting the NF-κB pathway. Importantly, the in vitro findings were consistent with the in vivo results, showing that oral administration of Ind significantly reduced tumour development in mice.[72]

A recent study investigated the anticarcinogenic effect of OFI juice, doxorubicin antibiotics, and their combination against breast cancer in rats. The effects of these treatments on liver functions, serum lipid profile, tumour biomarkers and histopathology of mammary gland tissue were also evaluated. The results showed that the treatments, including OFI juice, doxorubicin and their combination, improved liver functions and lipid profile. Additionally, tumour biomarkers, such as alpha-fetoprotein, tumour necrosis factor alpha, nuclear factor kappa B and circulating collagen type IV, were decreased by the treatments. Microscopic examination of mammary gland tissues from the treated rats, particularly those receiving the combination treatment, revealed nearly normal mammary acini and lobules, indicating a potential reversal of malignancy-associated changes. These findings suggest that OFI juice, doxorubicin and their combination may have anticarcinogenic effects against breast cancer in rats 2022.[73]

Apart from individual inhibitory effects on cancer cell growth, phytochemicals have the potential to exert synergistic effects when combined with other phytochemicals or conventional anticancer drugs. A recent study conducted by Allegra et al. assessed the effects of combining Ind, a pigment derived from OFI fruit, with CCDP against cervical cancer cells (HeLa). Cell viability was measured using a Trypan blue assay, and cell morphology was examined using fluorescence microscopy. Apoptosis, cell cycle distribution, MMP and cell redox balance were assessed through flow cytometry. The expression levels of apoptosis-related proteins were analysed using western blotting. The combined treatment showed significant effects ($P < 0.05$) on several cellular processes compared to the individual treatment groups, including phosphatidylserine externalisation, cell morphological changes, cell cycle arrest and decrease in MMP and ROS production. The combined treatment increased the production of ROS and decreased GSH levels. Furthermore, the combined treatment resulted in the overexpression of pro-apoptotic proteins, including Bax, cytochrome c, p53 and p21waf1, while the expression of BCL-2 was downregulated.[74]

The role of OFI extracts in reducing the side effects of several chemotherapeutic medicines used in the treatment of several types of cancers has also been examined. A study demonstrated that the OFI fruit extract could mitigate CCDP-induced renal toxicity in mice by exerting antioxidant and renoprotective effects. The presence of compounds, such as myricetin, quercetin and luteolin, in the extract likely contributed to its observed benefits in protecting the kidneys from CCDP-induced damage.[75] Another study investigated the potential protective effects of OFI ethanolic extract on testicular damage induced by methotrexate in rats. Methotrexate is a chemotherapeutic drug used in cancer and inflammatory disease treatment, but it can have detrimental effects on rapidly dividing cells. Treatment with OFI extract showed protective effects on testicular histology, oxidative stress markers and sperm parameters (count and motility).[76]

Based on studies discussing the antiproliferative and apoptotic-inducing effects of compounds derived from OFI, as well as their synergistic effects with other phytochemicals or

conventional anticancer drugs and their ability to reduce the side effects of certain chemotherapeutic drugs, it can be concluded that OFI extracts have significant potential as sources of naturally occurring bioactive compounds with anticancer properties.

## Conclusion

Utilising naturally occurring bioactive compounds from OFI as a starting point for cancer drug development offers several advantages. These compounds are derived from a natural source and may possess favourable safety profiles compared to synthetic compounds. Additionally, they often exhibit complex chemical compositions, potentially leading to synergistic effects and multiple modes of action. Further research and exploration of OFI extracts and their bioactive components are warranted to fully understand their mechanisms of action, optimise their efficacy and evaluate their safety in preclinical and clinical settings. Nonetheless, the findings discussed in this review provide a strong foundation for considering OFI extracts as valuable resources for the development of cancer drugs.

## Acknowledgments

None.

## Conflicts of Interest

The authors declare no conflicts of interest.

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