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REVIEW ARTICLE

Opuntia ficus indica (L.) Mill. An Ancient Plant Source of Nutraceuticals

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Abstract: *Opuntia ficus-indica* (L.) Mill. (OFI) is a plant with numerous beneficial properties known in traditional medicine. It has been a domesticated plant in Latin America, Africa, Mediterranean countries, the Middle East, India and Australia. Nowadays, the research concentrates on natural compounds to lower costs and the possible side effects of synthetic compounds. The use of nutraceuticals, bioactive compounds of vegetable origin with important nutritional values, is encouraged. OFI has shown numerous activities due to its high content of antioxidants, including flavonoids and ascorbate, pigments, carotenoids and betalains, phenolic acids and other phytochemical components, such as biopeptides and soluble fibers. The most important effects of OFI are represented by the activity against acne, arthrosis, dermatosis, diabetes, diarrhea, fever, high blood pressure, prostatitis, rheumatism, stomachache, tumor, wart, allergy, wound, colitis and some viral diseases. Moreover, a promising role has been suggested in inflammatory bowel disease, colitis and metabolic syndrome. The most recent studies addressed the role of OFI in preventing and treating COVID-19 disease. In light of the above, this review summarizes the biological activities and health benefits that this plant may exert.

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Keywords: *Opuntia ficus-indica*, Nutraceuticals, Cactus pear, Prickly pear, Health, Bioactive compounds.

1. INTRODUCTION

The *Opuntia* genus of plants is native to the American continent; up to now, 377 species have been recognized, and 104 have been wild in Mexico, 60 of which are endemic to this country [1]. It had a significant role in the agricultural economy and diet of the ancient Mexicans of the Aztec empire and is now distributed in different countries and all continents. Cactus Pear or Prickly Pear (*Opuntia* spp., Cactaceae) is a tropical or subtropical plant, invasive, widespread and well adapted to arid and semi-arid zones such as the Mediterranean area [2]. It has been a domesticated plant in Latin America, Africa, Mediterranean countries, the Middle East, India and Australia. Differences in the phytochemical composition exist between wild and domesticated species [3]. Cactus pear may be used as a crop for subsistence and market-oriented agriculture, contributing to the food security of the population in agriculturally marginalized areas [4]. It is used for fighting against desertification and as a reserve in arid and semi-arid lands and seasonal or year-round fodders. It can also improve soil properties and prevent erosion [5]. Particularly, *Opuntia ficus-indica* (L.) Mill (OFI), shown in Fig. (**1**), is a commercial plant cultivated on a considerable surface in some countries, including Mexico, Italy and South Africa. In Mexico, the nutritional properties of OFI have been known since ancient times, and fresh cladodes are used for human consumption as "nopales." Only in Mexico, more than 3 million hectares are used to crop OFI for human consumption. The cladodes can be eaten raw, boiled or grilled. The mucilage extracted from pruned cladodes is a source of carbohydrates and fibers [6] and is considered an auxiliary to reduce the glycemic and cholesterol levels in human blood [7, 8]. The prebiotic potential of cladode's powder and its derived products has been recently described, too [9]. The starting material is easily available and can interact with the industrial mass production at different levels of the markets, such as food, pharmaceutical and nutraceutical, but also with the local companies, as it may be present in the lands of the farmers. It is used as a nutritional and pharmaceutical agent in several dietary and value-added products and as a food source for animals and humans [10]. Moreover, it finds application in the food industry. Cactus pear fruit is commonly consumed fresh, but it can also be consumed as juices, jam, syrups,

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jelly, wine, vinegar, and other processed products. These products are widely employed in Latin America. Recent studies demonstrated that adding juices from cactus pear and pomegranate to stirred yoghurt milk significantly improved its quality and health benefits [11-13]. OFI shows several interesting biological activities [13-17] for the high content of antioxidants (flavonoids, ascorbate), pigments (carotenoids, betalains), and phenolic acids. In addition to these nutraceuticals, other phytochemical components (biopeptides, soluble fibers) have been characterized and contribute to the medicinal properties of *Opuntia* spp. OFI has been reported to be effective against acne, arthrosis, dermatosis, diabetes, diarrhea, fever, high blood pressure, prostatosis, rheumatism, stomach ache, tumor, wart, allergy, wound, colitis and some viral diseases [18]. A promising role of OFI has been suggested in inflammatory bowel disease (IBD) treatment and colitis [19, 20]. Among the numerous beneficial activities of OFI, recently also, the ultraviolet (UVA) photoprotective properties have been described [21], as well as its potential antiobesity nutraceutical action [22] and its activity in metabolic syndrome [23]. Recent studies also aimed to study the bioactive compounds in *Opuntia* spp. wastes as a new source of nutraceuticals [24]. The cladode of the plant is traditionally used to treat gastritis, intestinal colic and ulcers [25]. The urgent need for treatments for Coronavirus Disease 19 (COVID-19), caused by the Severe Acute Respiratory Syndrome (SARS)-Coronavirus (CoV)-2 [26], justifies the great attention currently being paid to repurposed antiviral drugs [27], and also to natural products and herbal medications [28]. In this regard, the antiviral properties of some *Opuntia* spp components have been recently reported, paving the way to deepen the studies, particularly inherent the COVID-19 [29]. Moreover, the sedative and anxiolytic activity for OFI recently described in mice could be an interesting advantage for using this plant in COVID-19 patients [30]. This review is focused on the phytochemistry, nutritional value and countless health benefits of OFI.

Fig. (1). *Opuntia ficus indica* (L.) Mill. parts. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. *OPUNTIA FICUS-INDICA* (L.) MILL (OFI)

Opuntia ficus-indica (L.) Mill (OFI) (Family Cactaceae, subfamily Opuntiodeae, Genus *Opuntia*, subgenus *Platyopuntia*) is a commercial plant cultivated on considerable surfaces for industrial ends in some countries, including Mexico, Italy and South Africa. Particularly, in Mexico, it spreads on a surface of 300.000 ha [31]. In North Africa, the cultivation of OFI is used both for preventing soil erosion in arid areas and as a forage substitute in periods of drought [32]. The enhancement of arid zones and the decrease of water resources have gained importance to *Opuntia* spp. as a useful source. The stems of OFI are formed by groups of opaque-green cladodes with areolas that contain numerous thorns; they produce large yellow-orange flowers and edible fruits. The fruits can change in colour from green-yellow (less sweet) to reddish-purple (very sweet) and orange shades between them. OFI fruits are used as a laxative in Turkey to reduce kidney stones and rheumatism pains and as a sedative [33]. The young cladodes of OFI, also known as nopalitos, are consumed as vegetables, containing polyphenols such as ruthin, iso-quercitrin, narcissin and nicotiflorin [34] and a series of polysaccharides, such as pectins with high molecular weight and important functional properties such as rheological, medicinal and nutritional ones [35]. The cladodes are perishable and have a very short storage life, from 5 days at room temperature to 10 days in refrigerated environments [36]. In the fruits, pigments named betalains are present, which are widely distributed in the *Cactaceae* family. Studies with several species of Opuntia fruits have revealed a high betalains' content [37]. Both cladodes and fruits have a high percentage of pectins and fibers, which can increase fecal mass and intestinal motility, affecting cholesterol and glucose plasma levels; as reported in the literature, fruits and stems of *Opuntia* have been traditionally used in oriental folk medicines to treat diabetes, hypertension, burns, edema and indigestion. It has also been reported that the extracts of fruits or stems exhibit hypoglycemic, antiulcer, antiallergic, analgesic and antioxidant activity [38]. Moreover, cladodes of the plant contain neutral mucilage (glucomannan) that delays glucose absorption and interferes with lipid metabolism [39]. β-Sitosterol, an active anti-inflammatory principle, was isolated from the fruits and the stem extracts; fruit and flower infusions significantly enhance diuresis [40]. Cactus juice was demonstrated to prevent the negative effects of nickel chloride [41]. In the liver, nickel chloride-induced oxidative stress is evidenced by increased lipid peroxidation and changes in antioxidant enzyme activities. Superoxide-dismutase (SOD) activity was found to be increased, whereas glutathione peroxidase and catalase activities were decreased. These changes did not occur in animals previously given cactus juice, demonstrating a protective effect of this vegetal extract [42]. Betacyanins, one of the main components of OFI, are pigments also related to the preventive action against several diseases like inflammatory, cardiovascular diseases, rheumatoid arthritis, leukemia, and cancer and protect against acetaminophen-induced acute liver failure [43, 44].

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3. COMPOSITION

The composition of OFI has been recently reported in detail [45, 46]. There are several differences in the content of pulp and peel. Cactus pear fruit pulp has a higher content of proteins, lipids and moisture but lower total fiber and ash content than the peel. Glucose and fructose are the predominant sugars in both peel and pulp (glucose and fructose: 123 g/L and 71.7 g/L in pulp and 91.0 g/L and 52.0 g/L in the peel) [47]. The mineral content of cactus pear fruit is essentially due to potassium, followed by calcium and magnesium and sodium. Iron, manganese and copper are the major microelements in fruit peel and pulp. The bioactive compounds are represented by vitamin C, flavonoids, betalains (betanin and indicaxanthin), carotenoids and polyphenols and are present in fruit peel and pulp (Tab. 1). Betalains are water-soluble nitrogenous pigments, they can be divided into two major structural groups, the red to red-violet betacyanins (Latin *Beta*, beet and Greek *kyanos*, blue color) and the yellow betaxanthins (Latin *Beta* and Greek *xanthos*, yellow). Betacyanins can be further classified by their chemical structures: betanin-type, amaranthin-type, gomphrenin-type and bougainvillein-type [37]. They are responsible for the red or yellow color of fruits, flowers, roots and leaves of plants belonging to the *Cactaceae* family [48]. Various colors characterize cactus pear fruits due to the combination of the two betalain pigments: betanin, purple-red, and indicaxanthin, yellow-orange. Vitamin C is an essential nutrient for humans and other vitamins that provide high antioxidant activity and prevent against oxidative stress in humans [49]. Flavonoids are a group of secondary metabolites of plants implicated in fruit and flower coloration, photosensitization and energy transfer. Flavonoids present high antioxidant activity that helps to neutralize damaging free radicals and to prevent oxidative stress in the human body [50]. Cactus pear fruits contain more flavonoids in the peel than in the pulp, and there are fewer flavonoids than phenolic compounds. The most represented are kaemferol and isorhamnetin (Table **1**). Carotenoids, known antioxidants, belong to isoprenoid pigments and are widely distributed among fruits. They are responsible for most yellow, orange and red colors in vegetables, thus contributing to the appearance and attractiveness of a fruit [51]. Polyphenols, among which resveratrol is commonly mentioned [52], are an important group of natural compounds found in plants and characterized by the presence of more than one phenolic moiety. These compounds help to prevent degenerative diseases, cardiovascular diseases and cancers due to their antioxidant activity [53]. The peel of cactus pear fruits is generally richer in total phenolic content than the pulp. Generally, predominant compounds in cactus pear fruit pulp and peel are ferulic acid and derivatives, isorhamnetin and derivatives, sinapic acid and derivatives, quercetin and derivatives. Recently, the anti-inflammatory opuntiol (6-hydroxymethyl-4-methoxy-2*H*-pyran-2-one) has been isolated from OFI [54], whereas it had been previously found in *Opuntia dellinii* [55]. Other compounds present in low amounts are rosmarinic acid, myricetin, luteolin, catechin, naringin, syringaresinol, and *p*-coumaric acid. They are summarized in Table **1** [56-68].

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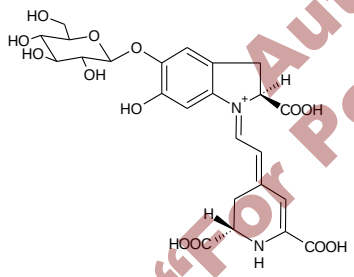
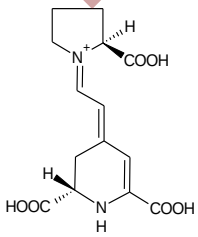
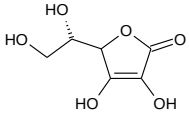
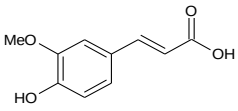
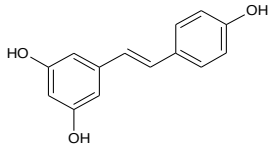
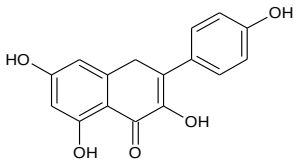
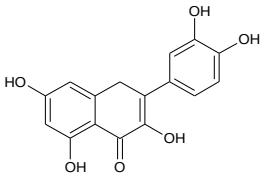
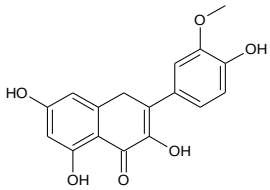
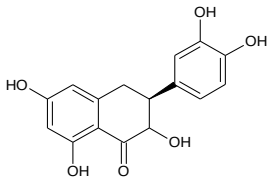
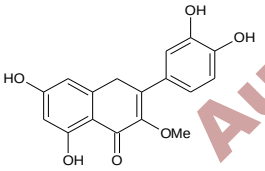
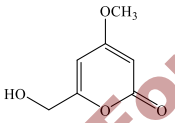
Table 1. Structure of most abundant compounds present in OFI.

	Betanin	[34, 48, 60]
	Indicaxanthin	[49, 61, 62, 90]
	Vitamin C	[49]
	Ferulic acid	[51, 53]

(Table 1) contd…

	Resveratrol	[51, 52]
	Kaempferol	[51]
	Quercetin	[51, 53, 63]
	Isorhamnetin	[51, 53, 64-66]
	Dihydroquercetin	[63]
	Quercetin 3-methyl ether	[63]
	Opuntiol	[54, 55, 67, 68]

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4. PHARMACOLOGICAL ACTIVITIES

Several pharmacological activities have been described for OFI. They are briefly detailed below and summarized in Table **2** [69-96].

4.1. Antiulcer Activity and Action on Digestive Disturbances

In Sicily folk traditional medicine, OFI cladodes are used to cure gastric ulcers [97]. When OFI cladodes are administered as a preventive therapy, they keep the gastric mucosa in normal conditions by preventing mucus dissolution caused by ethanol and favoring mucus production. Mucus production also increases during the curative treatment. The treatment with OFI cladodes provokes an increase in the number of secretory cells. The gastric fibroblasts seem to be involved in antiulcer activity [69]. In another work, the juice of whole fruits of Sicilian cultivars of OFI was investigated. Ethanol-induced contraction of gastric smooth muscle in rats was shown to be prevented by OFI fruit juice. An increase in mucus production and the restoration of the normal mucosal architecture were evidenced by light microscopy observations [70]. The major components of cladodes are carbohydrate polymers, mainly mucilages and pectin. The cytoprotective effects were induced by cladodes and may be attributed to mucilages and not significantly to pectin [98]. OFI oil extracted by cold pressing has been recently shown to be effective in healing full-thickness skin injury and as an antimicrobial against bacteria, fungi, and yeast [71]. Then, the preventive and curative effects of OFI var *inermis* seed oil extracted by cold pressing were investigated on an ethanol-induced gastric ulcer model in Wistar rats pretreated before ethanol gavage. OFI oil exhibited high efficiency in protecting the cytoarchitecture and function of

Table 2. Principal pharmacological activities of OFI extracts.

Antiulcer Activity and Action on Digestive Disturbances		
Plant Parts	**Pharmacological Activities**	**Refs.**
Cladode	Prevention of mucus dissolution caused by ethanol and mucus production	[69]
Fruits juice	Prevention in an ethanol-induced contraction of gastric smooth muscle in rats	[70]
Oil extracted by cold pressing	- Effective in the healing of full-thickness skin injury - Antimicrobial against bacteria, fungi, and yeast - Protection of the gastric mucosa in ethanol-induced gastric ulcer model in Wistar rats	[71, 72]
Juice	The laxative effect of gastrointestinal transit in healthy and constipated-rats	[73]
Seeds aqueous extract	Antidiarrhoeal activity	[73]
Mature cactus pear juice	Increase in gastrointestinal transit (presence of few **tannins**)	[74]
Green cactus pear juice	Decrease in gastrointestinal transit (presence of more **tannins**)	[74]
Antimicrobial Activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Cladode	*Escherichia coli* MBC= 4 mg/mL *Staphylococcus aureus* MBC= 1 mg/mL	[75]
Methanol and chloroform cladodes extracts	*Streptococcus pneumoniae* *Bacillus subtilis*	[76]
Mature cladode extract	*Staphylococcus aureus* and *Enterococcus faecalis* MIC = 1500 g/mL	[77]
Immature cladode extract	*Staphylococcus aureus* and *Enterococcus faecalis* MIC = 1000 g/mL	[77]
Antiviral activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Cladode	Antiviral activity against *Cucumber mosaic* virus due to the presence of antiviral proteins Opuntin A and Opuntin B	[78]
	Antiviral activity against SARS-CoV-2 related to the presence of the chiral phytochemical astragalin	[28]
Ethanol plant extracts	Antiviral activity against Peste des Petits ruminant virus	[79]
Anti-inflammatory Activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Plant extracts	Prevention of collagen I and III breakdowns in UVA radiation-exposed mouse skin related to the presence of opuntiol	[67]
	Reduction of the inflammatory response to stressful stimuli	[80]
Juice	Decrease in erythrocytes damages induced by ethanol administration and/or abuse	[81]
Anticancer Activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Seed oil	Apoptosis in primer colon adenocarcinoma (Colo-320) cell lines	[82]
Cactus pear mixture aqueous extract	Reduction in cancer cells growth and apoptosis in ovarian cancer cells	[83]

(Table 2) contd…

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Plant Parts	Pharmacological Activities	Refs.
Plant extracts	Antiproliferative activity against PC3 prostate and mammary MCF-7 cell lines	[84]
	- Apoptosis in metastatic human colon cancer cells (HT-29) - Mitochondrial damage and ROS levels increase related to the presence of isorhamnetin glycoside	[66]
	The presence of **opuntiol** induces: - Cells growth inhibition and apoptosis in human glioblastoma multiforme (GBM) cell lines U87 - Antiproliferative activity in KB oral carcinoma cells	[54, 68]
	Antiproliferative effect against A375 human melanoma cell lines and in a mice model of cutaneous melanoma related to the presence of indicaxanthin	[61]
Antioxidant, neuroprotective and hepatoprotective activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Fruit and stem	Neuroprotective effect against oxidative neuronal injuries induced in primary cultured rat cortical cells related to the presence of quercetin, (+)-dihydroquercetin, and quercetin 3-methyl ether	[63]
***n*-Butanolic extract**	Enhancement of long-term memory in mice	[85]
Cladodes	Protective effect against UVA-induced oxidative stress in normal human keratinocytes	[86]
Peels and flowers	Antioxidant activity was evaluated using different assays (DPPH, RP, HPSA, ORAC, TEAC, LOX-FL)	[60, 87]
Fruit extract	Reduction in hepatic damage by alcoholic oxidative stress related to the presence of **(+)-taxifolin**	[88]
Juice	Capacity to end free radical chain reactions or to enhance endogenous antioxidant activities	[89]
	Activity in Central Nervous System (CNS)	
Plant Parts	**Pharmacological Activities**	**Refs.**
Fruits extract	Strong sedative and hypnotic activities related to the presence of isorhamnetin, isorhamnetin 3-*O*-glycoside, isorhamnetin 3-*O*-rutinoside, and kaempferol 3-*O*-rutinoside	[30]
Antidiabetic, Antiobesity and Antihypertensive Activity		
Plant Parts	**Pharmacological Activities**	**Refs.**
Cladode	Glucose lowering effects	[90-92]
Nopalito	Ameliorate blood pressure and glucose homeostasis	[93]
Flowers, fruit and cladodes infusion	Diuretic, natriuretic and antiuric activities	[94, 95]
Cladode gel and aqueous extract	Diuretic and hypotensive effect on normotensive rabbits without deterioration in renal function test	[96]

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the gastric mucosa against the severe damages provoked by ethanol intake. Specifically, the effect of OFI var *inermis* oil was compared with two allopathic reference drugs, sucralfate and ranitidine. It was administered per os (p.o.), 3.5 mL and 7 mL of OFI oil/kg/body weight (bw). A major protection was evidenced with dose 2 (7 mL/kg/bw) compared to dose 1 (3.5 mL/kg/bw) [72]. Other varieties of OFI have shown antiulcerogenic activity in rats, such as prickly pear cactus OFI var. *saboten* fruit juice in Sprague–Dawley rats. Particularly, OFI var *saboten* fruit juice and maltodextrin, at oral doses of 800 and 1600 mg/kg, significantly reduced stress lesions (800–1600 mg/kg) [99]. Moreover, OFI var. *saboten* dried stem powder possessed pronounced inhibitory activity on gastric lesions without showing antiulcer activity in male Sprague-Dawley rats. It showed significant inhibition in HCl·ethanol-induced gastric lesions at 200 and 600 mg/kg p.o. and in HCl·aspirin-induced gastric lesions at 600 mg/kg p.o. The same powder also showed significant inhibition in indomethacin-induced gastric lesions at 200 and 600 mg/kg doses, p.o [100]. OFI showed different activities in digestive disturbances in rats. It is interesting to note that juice and aqueous extract of the seeds showed a reverse effect. Indeed, the juice at various doses has a laxative effect on gastrointestinal transit in healthy and constipated-rats, whereas the aqueous extract of the seeds leads to a reduction of motility in normal rats giving it a remarkable antidiarrhoeal activity, a notable intestinal fluid accumulation decline and electrolyte concentrations reestablishment. Moreover, orally juice administered at different doses accelerated the stomach emptying time compared to the seeds' aqueous

extract. More importantly, a significant variation in the phytochemical constituent levels between juice and seeds was found. These findings confirm this fruit's reverse therapeutic effects in treating digestive disturbances such as difficulty stool evacuation and massive intestinal secretion, as well as the gastric emptying process perturbation [73]. However, the cactus pear juice at two distinct phases of maturity has different phytochemical characteristics and opposite effects on gastrointestinal physiological actions in rats. It was found that the juice of mature fruit increases gastrointestinal transit (GIT) significantly and dose-dependently. In contrast, the green fruit causes the inhibition of this process. These data confirm that the cactus pear fruit is characterized by dissimilar chemical composition. This observation seems to be related to tannins, polyphenols possessing an astringent property. In an advanced stage of maturity, the tannin content in prickly pear fruit juice was demonstrated to be decreased [74].

4.2. Antimicrobial Activity

The antimicrobial activity of OFI against gram-positive and gram-negative bacteria and biofilms has been recently reviewed [101]. Sánchez *et al.* described the antimicrobial activity of *Opuntia* cladodes against *Escherichia coli* and *Staphylococcus aureus* with a minimum bactericidal concentration (MBC) of 4 mg/mL and 1 mg/mL, respectively [75]. Methanol and chloroform extracts were active against *Streptococcus pneumoniae* and *Bacillus subtilis* [76]. The mature cladode extract of OFI at the concentration of 2000 g/mL was active against gram-negative bacteria (*Escherichia coli*, *Salmonella typhimurium* and *Enterobacter aerogenes*), whereas the immature cladode extract was more effective and showed activity even at a concentration of 1500 g/mL. Minimum inhibitory concentration (MIC) values for two Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) [102, 103] were 1500 g/mL for mature cladode extract and 1000 g/mL for immature one [77]. Recently, fruit peel has been studied for its anti-pneumonia activity. The authors demonstrated that the valuable constituents contained in the unused waste from prickly pear fruits have beneficial potential against pneumonia pathogens [104].

4.3. Antiviral Activity

The antiviral activity of OFI has been described in the literature [105, 106]. OFI cladode has significant antiviral activity against the *Cucumber mosaic* virus (CMV belonging to the Bromoviridae family). This activity seems related to the antiviral proteins Opuntin A and Opuntin B [78]. The same authors recently demonstrated that these proteins exhibit ribonuclease activity [107]. Moreover, the anti-COVID-19 utility of OFI as a source of potential antiviral drugs has been investigated based on the activity of some of its phytochemical constituents. The antiviral activity seems related to the chiral phytochemical astragalin [28], thus underlying the importance of chirality in pharmacological activities [108, 109]. The ethanol extract of OFI was found to exert antiviral activity against Peste des Petits ruminant virus, an enveloped virus with RNA as its genetic material and belongs to the genus *Morbillivirus* [79].

4.4. Anti-inflammatory Activity and Activity in Alcohol Hangover

The anti-inflammatory activity of OFI has been known for more than two decades [110, 111]. Studies on OFI determined that this activity seems to be related to flavonoids [112], particularly to isorhamnetin glycosides [64, 65] and β-sitosterol [113], or to indicaxanthin [114]. Recently, OFI activity against UVA radiation-mediated inflammation and skin photoaging was studied in experimental animals. It was shown that opuntiol prevented collagen I and III breakdowns in UVA radiation-exposed mouse skin by inhibiting inflammatory responses, MAPK activation, and degradation of matrix collagen molecules [67]. OFI is particularly interested in the treatment of alcohol hangovers [13]. It is known that the symptoms of the alcohol hangover are largely due to the activation of inflammatory processes. An extract of the OFI plant has been demonstrated to diminish the inflammatory response to stressful stimuli [80]. OFI juice is useful for decreasing damages to erythrocytes induced by ethanol administration and/or abuse. The release of acetaldehyde in the blood causes erythrocyte abnormality and fragility, for which OFI juice might have a protective effect [81].

4.5. Anticancer Activity

Medicinal plants are widely used as anticancer agents [115-117]. Cactus pear is widely studied for its anticancer properties [118]. OFI seed oil may have an anticancer effect on primer colon adenocarcinoma (Colo-320) cell lines by inducing apoptosis [82]. Cactus pear mixture aqueous extract was also shown to reduce ovarian cancer cell growth by inducing apoptosis [83]. Recently, the *in vitro* and *in vivo* antiproliferative activity of extracts of OFI has been demonstrated against PC3 prostate and mammary MCF-7 cell lines [84]. OFI has also been shown to induce apoptosis in metastatic human colon cancer cells (HT-29). This activity seems to be due to isorhamnetin glycoside through mitochondrial damage and the increase of ROS levels [66]. The anticancer activity seems related to the total phenolic content [119]. It must be considered that there are intervarietal differences among prickly pears in terms of juice properties and phytochemicals. Moradillo (*Opuntia Violaceae*) variety, containing a high amount of flavonoids, diminished both prostate and colon cancer cells viability without affecting mammary or hepatic cancer cells, while Rastrero (*Opuntia rastrera*) reduced the growth of several cancer cell lines without affecting normal fibroblasts viability [120]. Recently, opuntiol has been investigated for its antiproliferative activity. It has been shown to inhibit growth and induce apoptosis in human glioblastoma multiforme (GBM) cell lines U87 by up-regulating active caspase 3 expression [68]. It also shows antiproliferative activity in KB oral carcinoma cells [54]. Several reports show the benefit of indicaxanthin in the treatment of cancers. It showed an antiproliferative effect against A375 human melanoma cell lines and a mice model of cutaneous melanoma *via* inhibiting the NF-κB pathway

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[61]. Moreover, combining indicaxanthin with cisplatin gave interesting results against cervical cancer HeLa cells [62].

4.6. Antioxidant, Neuroprotective and Hepatoprotective Activity

Neuroprotective and antioxidant effects of OFI have been extensively studied for the var. *saboten.* The protective effect against oxidative neuronal injuries induced in primary cultured rat cortical cells by OFI var. *saboten* and the antioxidant activity was described by Dok-Go *et al.* using three different cell-free bioassays [63]. The results indicate that quercetin, (+)-dihydroquercetin, and quercetin 3-methyl ether were the active antioxidant principles in the fruits and stems of OFI var. *saboten* exhibiting neuroprotective actions against the oxidative injuries induced in rat cortical cell cultures. Quercetin 3-methyl ether seems to be the most potent neuroprotectant of the three flavonoids. The *n*-butanolic extract of OFI var. *saboten* Makino enhanced long-term memory in mice [85]. OFI cladodes also protect against UVA-induced oxidative stress in normal human keratinocytes [86]. In general, the antioxidant activity seems related to the cultivar used [121]. A recent study showed that OFI peel and flower teas exhibited high antioxidant activities measured by several tests, such as 1,1-diphenyl-2-picrylhydrazyl radical (DPPH•), reducing power (RP), and hydrogen peroxide scavenging activity (HPSA). They also showed antiacetylcholinesterase activity that was higher in flowers than in peel teas [87]. The *in vitro* antioxidant capacity of OFI (var. *fresa*, *colorada* and *blanco*) and *Opuntia stricta* var. *dillenii* has been recently studied by traditional antioxidants (ORAC and TEAC) and lipoxygenase-fluorescein (LOX-FL) methods. The latter, LOX-FL, showed the highest antioxidant capacity correlated with betanin content [60]. OFI is also considered a plant with a hepatoprotective capacity [122]. OFI fruit extracts were demonstrated to reduce hepatic damage by alcoholic oxidative stress. This activity seems related to the flavonoid (+)-taxifolin. Effects on cellular reduced glutathione (GSH) and related enzymes indicated that the hepatoprotective activity of (+)-taxifolin might be due to maintaining the level of GSH [88]. The hepatoprotective effects of OFI juice were also demonstrated. *Opuntia ficus indica* f. *inermis* juice activity seems to be due to its ability to end free radical chain reactions or enhance endogenous antioxidant activities [89]. Other studies attributed the hepatoprotective activity to lignans. A furofuran lignan exhibits antioxidative and hepatoprotective effects by inducing HO-1 protein expression in HepG2 human liver cells [123].

4.7. Activity in the Central Nervous System (CNS)

Recent studies report the sedative, anxiolytic and hypnotic activity exerted by OFI. Akkol *et al*. (2020) [30] describe a study, in mice, of a crude methanolic extract of OFI fruits, which was sequentially fractionated into five subextracts: *n*-hexane, dichloromethane, ethyl acetate (EtOAc), *n*-butanol, and water. The most active subextract was the EtOAc one, which showed strong sedative and hypnotic activities, assessed by an open-field test for the former and a thiopental-induced sleeping test for the latter. The major components of the extract were isorhamnetin, isorhamnetin 3-*O*-glycoside, isorhamnetin 3-*O*-rutinoside, and kaempferol 3-*O*-rutinoside identified using spectral techniques. In some regions of Brazil, OFI is considered a non-traditional food, where the population is food-insecure and has a low socioeconomic background [124]. A recent study analyzed an OFI beverage as a non-traditional food, considering the sensory properties, expectations, experiences, and emotions of low-income and food-insecure Brazilian potential consumers. Results showed that OFI beverages generally evoked positive emotions after tasting [125].

4.8. Antidiabetic, Antiobesity and Antihypertensive Activity

The protective effect of OFI in type 2 diabetes (T2D) has been demonstrated [90, 91]. Juice from the cladodes is used in African traditional medicine to treat diabetes and wound infections [92]. The glucose-lowering effects are likely due to cladodes, whereas there is a lack of evidence to support the recommendation of using *Opuntia* spp. fruit products as an alternative or complementary therapy in reducing risk or managing T2D [126]. OFI nopalitos may be used to manage diabetes mellitus and its complications. In high-fat diet (HFD)/streptozocine (STZ)-induced T2D rats, they were demonstrated to ameliorate blood pressure and glucose homeostasis to improve reverse cholesterol transport by increasing lecithin cholesterol acyltransferase (LCAT) activity and attenuating lipid peroxidation in tissues by enhancing enzymatic antioxidant defense [93]. Recently, Sirotkin has published a comprehensive and interesting review on OFI, underlying its effects on fat and obesity in animals and humans due to the inhibition of fat generation and oxidation. However, its applicability as an anti-obesity nutraceutical requires further clinical studies [22]. Galati *et al.* reported that flower infusion shows a modest increase in diuresis and natriuresis [94]. The fruit infusion instead had diuretic and anti-uric activity. The diuretic action observed may depend on stimulation of the urinary tract and is linked to the activation of neurohumoral mechanisms, mediators of stimuli acting on glomerules, or the pyelo-ureteral peristalsis [96]. Gel and aqueous extract of OFI cladode were demonstrated to have a significant diuretic effect on rats, and the lyophilized extract had a diuretic and hypotensive effect on normotensive rabbits without deterioration in renal function test. Moreover, OFI flower infusion is traditionally used as a diuretic agent [95].

4.9. Wound Healing Activity

The important activity exerted by OFI is shown by the promotion of wound contraction in delayed wound healing, a common health hazard [127]. OFI stems and cladodes showed promising wound healing properties in animal models [62, 128] and OFI seed oil from Tunisia in rats [64]. The wound-healing potential of two lyophilized polysaccharide extracts obtained from OFI cladodes, applied on large full-thickness wounds in the rat, was also reported [129]. Recent

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work demonstrated the wound healing activity of OFI seed oil and its self-nano emulsifying drug delivery system in a rat model of full-thickness skin excision [130].

CONCLUSION

The most abundant plants of the *Cactaceae* family belong to the genus *Opuntia* spp. They grow throughout America and the Mediterranean basin. OFI is the most representative of this family. Its fruit, known as cactus pear or prickly pear, is an oval berry grouped in different colors and constitutes valuable foodstuff for humans and animals in arid and semiarid regions. It is utilized in various food products such as juices, jams, syrups, witblits spirit and jellies. The oil extracted from OFI seeds seems to be a good potential source of edible oil for human and/or animal consumption. Nevertheless, the formidable spines studding the broad succulent cladodes must also be mentioned. Its nutritive value is due to its composition: protein, lipids, fibers, minerals, sugars, vitamin C, flavonoids, betalains (betanin and indicaxanthin), carotenoids and polyphenols. Its multiple pharmacological actions are well documented: antiviral, anti-inflammatory, anticancer, antioxidant and neuroprotective, antidiabetic and so on. This plant may be a good source of bioactive compounds for future pharmacological studies and the development of new supplements. Developing new strategies to ensure the valorization of the nutritional and functional potential of OFI and byproducts may be particularly interesting. This opens new perspectives for developing products with health benefits. Future research is needed to explore this ancient plant's additional benefits and promising properties.

LIST OF ABBREVIATIONS

CMV	=	Cucumber mosaic virus
CNS	=	Central Nervous System
COVID-19	=	Coronavirus Disease 19
DPPH•	=	1,1-Diphenyl-2-picrylhydrazyl radical
EtOAc	=	Ethyl acetate
GIT	=	Gastrointestinal transit
GSH	=	Glutathione
HFD	=	High-fat diet
HPSA	=	Hydrogen peroxide scavenging activity
IBD	=	Inflammatory bowel disease
LCAT	=	Lecithin cholesterol acyltransferase
LOX-FL	=	Lipoxygenase-fluorescein
MBC	=	Minimum bactericidal concentration
MIC	=	Minimum inhibitory concentration
OFI	=	Opuntia ficus indica (L.) Mill
ORAC	=	Oxygen radical absorbance capacity
RP	=	Reducing power
SARS	=	Severe Acute Respiratory Syndrome
SOD	=	Superoxide-dismutase
STZ	=	Streptozocine
T2D	=	Type 2 diabetes
TEAC	=	Trolox equivalent antioxidant capacity
UVA	=	Ultraviolet

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CONFLICT OF INTEREST

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