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REVIEW ARTICLE

Biopharmaceutical applications of *Opuntia ficus-indica*: bibliometric map, bioactivities and extraction techniques

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Abstract

Opuntia ficus-indica (OFI), widely recognized as prickly pear, is a native species from Mexico, being also widely distributed in many other geographical regions worldwide. OFI is a plant with numerous beneficial properties, provide that it is a source of dietary fibres, vitamins and many other bioactive compounds with anti-inflammatory, hypoglycemic and antimicrobial properties. Various parts of this plant including the fruit pulp and peel, cladode, and seeds are scientifically proven to have therapeutic potentials and are safe for human use. The bibliometric map of the works published since 2020 dealing with all aspects of OFI in the field of pharmacology, toxicology and pharmaceutics was generated, depicting the network of publications covering its ethnopharmacology, pharmacological properties, besides the extensive chemical characterization of the extracts, human and non-human uses, in vitro and in vivo studies, besides in silico tools. In this work, we review the scientific literature on the qualitative nutritional composition and bioactive compounds of prickly pear and its constituents, as well as its main biological activities and applications, also summarizing examples of extraction techniques commonly applied to different parts of the plant.

Keywords *Opuntia ficus-indica* (L.) Mill. · Prickly pear · Nopal cactus · Extraction techniques · Biopharmaceutical activities

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Introduction

Opuntia ficus-indica (L.) Mill. (OFI) commonly called prickly pear or nopal cactus, belongs to the dicotyledonous angiosperm *Cactaceae* family, a family that includes about 1500 species of cactus. *O. ficus indica* is a tropical and subtropical plant. It can grow in arid and semi-arid climates with a geographical distribution encompassing Mexico, Latin America, South Africa and Mediterranean countries [1].

The prickly pear plant is used nowadays in many forms, including food, feed, health and nutrition given its well-described pharmacological and nutritional values [2], being included in the composition of products such as cosmetics, tea, jam, juice and oil extracted from the seeds. Health benefits and biological activities have been reported for different parts of the prickly pear plant (Fig. 1A), such as fruit (Fig. 1B), cladodes (Fig. 1C), flower (Fig. 1D), seeds and seed oil [3]. Even the small seeds, squeezed, give a wonderful and precious anti-aging oil, rich in polyunsaturated fatty acids (over 80%) [4]. Figure 1 depicts relevant parts of the plant as source of ingredients for the production of several formulations.

Opuntia ficus-indica cladodes are a pale blue-green colour and are considerably larger (20–60 cm long) and firmly attached, giving it a tree-like structure and allowing it to reach up to 5 m in height [5]. The large cladodes of OFI have high concentrations of mucilage, which is a water-absorbing carbohydrate that allows the cladode to hold higher volumes of water [6]. This contributes to its success in ecosystems prone to drought [6].

While this species is globally cultivated and these domestic varieties are often free of glochids, wild OFI has small (10 mm long) glochids which return within several generations of escaping domestication [5]. The flowers of OFI are bright yellow, red or orange and can reach 9 cm in diameter [7, 8]. The colour of their fruit can also vary, showing similar colours to the flowers, and are mostly spineless or have spines that are very fine and easy to remove. Fruit maturation occurs in late summer for OFI, approximately 30–70 days after anthesis, and each fruit contains upwards of 200 viable seeds [9].

Tender cladodes of OFI are used as a food and in traditional Mesoamerican medicine to treat several conditions, such as asthma, cancer, diabetes, gastric mucosa diseases, heart conditions, hypercholesterolemia, hypertension, obesity, and rheumatic pain [10]. The cladodes contain high quantities of fiber, including mucilage, pectin, lignin, cellulose, and hemicellulose, substances that can bring well-being to the metabolism of lipids and sugars [11, 12]. Particularly important is the presence of β-polysaccharides (glucose units connected (1 → 4)-β bonds connected with (1 → 3)-β-bonds), characterized by an irregular structure that leads to a water-soluble structure [13]. This type of water-soluble fiber is capable of absorbing large quantities of water, and leads to the formation of viscous and gelatinous colloids which improve the absorption of many organic molecules.

Phenolic profile in cladode extracts was performed and flavonoids (anthocyanins, flavones, and flavonols) were the most abundant of polyphenols detected, followed by phenolic acids, lignans, alkylphenols, and stilbenes derivatives, showing high radical scavenging activity [14, 15].

The mucilage extracted from pruned cladodes is a source of carbohydrates and fibers, and is considered an adjuvant to reduce the glycemic and cholesterol levels in human blood [16]. The prebiotic potential of cladode's powder and its derived products have been recently described as well [17]. The starting material is easily available and is of interest for different markets, such as food, pharmaceutical and nutraceutical industrial mass production, but also for 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 [18].

Opuntia ficus-indica shows several interesting biological activities for the high content of antioxidants (flavonoids, ascorbate), pigments (carotenoids, betalains), and phenolic acids [3, 19–21]. In addition to these nutraceuticals, other phytochemical components (bio-peptides, soluble fibers) have been characterized and contribute to the medicinal properties of this plant. 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 [22]. A promising role of OFI has been suggested in inflammatory bowel disease (IBD) treatment and colitis [23, 24]. Among the numerous beneficial activities of OFI, recently ultraviolet (UVA) photoprotective properties have also been described [25], as well as its potential antiobesity nutraceutical action [26], and its activity in metabolic syndrome [27]. Recent studies also aimed to study the bioactive compounds in *Opuntia* spp. wastes as a new source of nutraceuticals [28]. The cladode of the plant is traditionally used to treat gastritis, intestinal colic and ulcers.

Today great attention is paid to the isolation of bioactive compounds from natural sources for their antioxidant properties. In particular, the interest is driven to the study and use of products obtained from the transformation processes of vegetable raw materials [29].

This review is dedicated to recent developments in medically relevant compounds isolated from *Opuntia ficus-indica*, and to potential biopharmaceutical applications

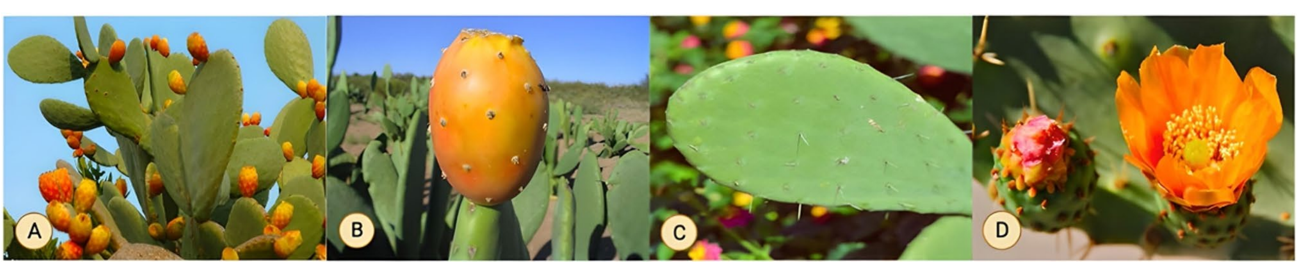

Fig. 1 Different anatomical parts of *Opuntia ficus-indica* (L.) Mill. **A** Overall plant; **B** Fruit; **C** Cladodes; **D** Flower and seeds

of the cactus in health promotion, disease prevention and therapy.

From a search on Scopus database using "*Opuntia ficus-indica*" as keyword, a total of 15 667 papers were listed in Scopus core collection since ever. Refining this search down to works published since 2020, we reduced the number to 6 190, among these 3 002 refer to the subject area of Agricultural and Biological Sciences, whereas only 595 refer to Pharmacology, Toxicology and Pharmaceutics.

To understand the main research topics the plant is being targeted, we have analyzed these latter using the VOSviewer software [30], and the resulting bibliometric map is shown in Fig. 2. A total of four clusters were generated, covering a good deal of bioactive ingredients used in ethnopharmacology, their pharmacological properties, besides the extensive chemical characterization of the extracts, human and non-human uses, in vitro and in vivo studies, as well as in silico tools.

Nutritional composition of *Opuntia ficus-indica*

Different methods have documented the nutritional value of *Opuntia* spp. Most of these studies match with respect to the differences among the phytochemical composition of their plant parts (fruits, roots, cladodes, flowers, seeds, and stems). These can be attributed to environmental

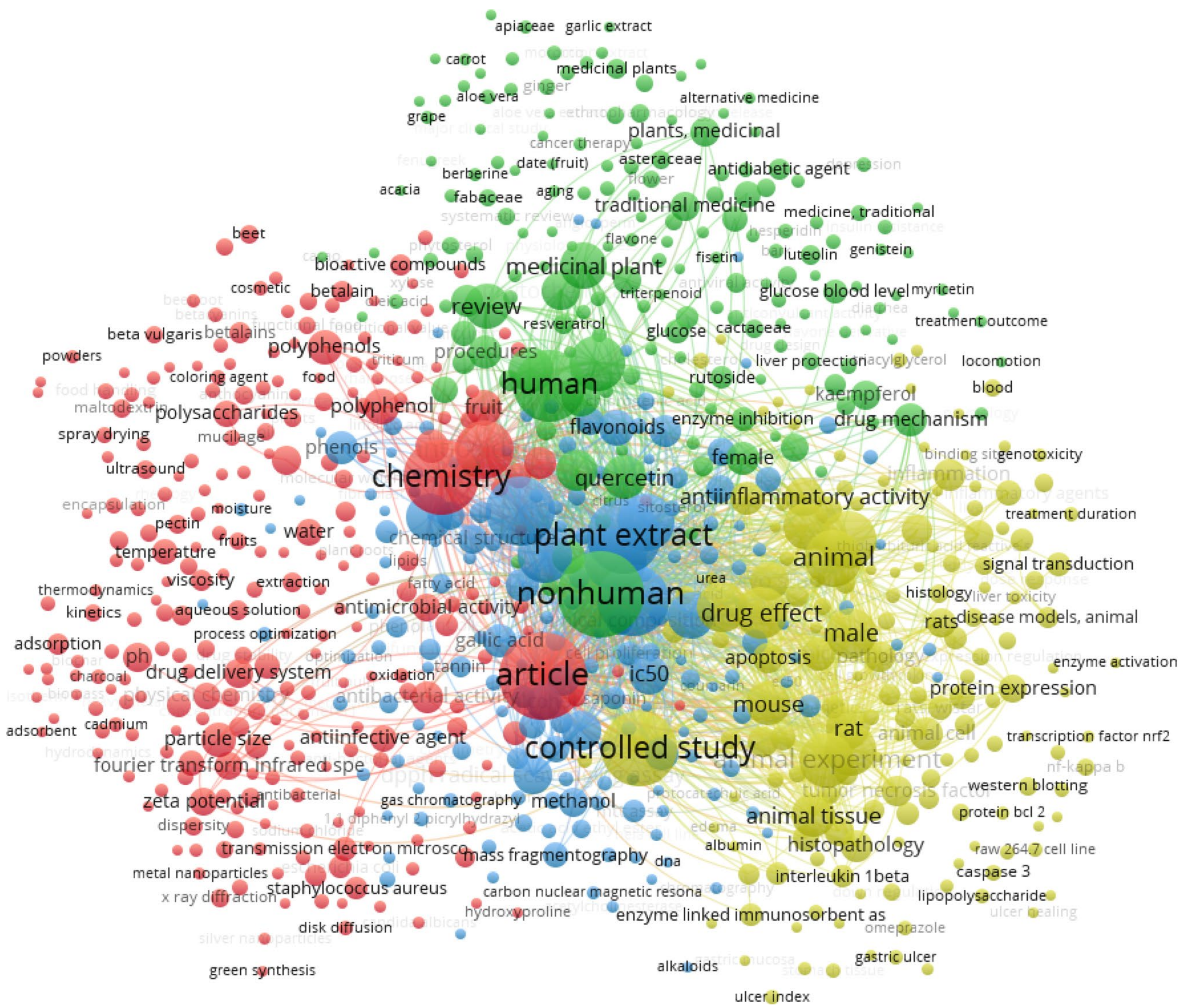

Fig. 2 Bibliometric map obtained by VOSviewer software version 1.6.16 (https://www.vosviewer.com), from papers indexed in Scopus published since 2020, using "*Opuntia ficus-indica*" as a single keyword, refined to the scientific discipline "Pharmacology, Toxicology and Pharmaceutics" (search: 5th April 2023). The minimum number of occurrences was set at 5, generating 772 terms meeting the threshold. Search of terms was done in manuscript abstract and keywords

conditions (climate, humidity), the type of soil that prevails in the cultivation sites, the age of maturity of the cladodes, and the harvest season [31–33], besides the geographical region and the extraction techniques that are used to obtain the extract and to isolate the bioactives from the different plant sources.

The nutritional qualitative composition of the different parts of *Opuntia ficus-indica* (L.) Mill. is summarized in Table 1 and has been recently reported in detail elsewhere [34, 35].

In general, opuntioid cacti contains a large amount of water (80 and 95%), carbohydrates (3–7%), proteins (0.5–1%), soluble fiber (1–2%), fatty acids (palmitic, stearic, oleic, vaccenic and linoleic) and minerals [Potassium (K), calcium (Ca), phosphorus (P), magnesium (Mg), chrome (Cr) and sodium (Na)]. They also have viscous and/or mucilaginous materials [made up of D-glucose, D-galactose, L-arabinose, D-xylose and polymers such as β-D-galacturonic acid linked to (1–4) and L-rhamnose residues linked with R (1–2)] whose function is to absorb and regulate the amount of cellular water in dry seasons [31–33, 36]. Among the main bioactive compounds of prickly pear, pigments (carotenoids, betalains, betaxanthins and betacyanins), vitamins (B1, B6, E, A, and C), flavonoids (isorhamnetin, kaempferol, quercetin, nicotiflorine, dihydroquercetin, penduletin, lutein), rutin, aromadendrine, myricetin vitexin, flavonones and flavanonols) and phenolic compounds (ferulic acid, feruloyl-sucrose and synapoyl-diglycoside) are highlighted [18, 19, 31–33, 36, 37].

Specifically, the cladodes and prickly pears fruits of OFI have shown several kinds of bioactive compounds, among which flavonoids (such as quercetin, kaempferol, isorhamnetin), essential amino acids (glutamine, arginine, leucine, isoleucine, lysine, valine and phenylalanine), vitamins (B1,

Table 1 Nutritional composition of the different anatomical parts of *Opuntia ficus-indica* (L.) Mill

Chemical species	Main component
CLADODES	
Minerals	K and Ca (mainly calcium oxalate crystals)
Vitamins	E, A, C, B1, B2, B3
Amino acids	Glutamine, arginine, leucine, isoleucine, lysine, valine and phenylalanine
Fatty acids	Palmitic acid, oleic acid, linoleic acid and linolenic acid
Carotenoids	Lutein, β-carotene and β-cryptoxanthin
Flavonoids	Quercetin, kaempferol, isoquercetin, isorhamnetin-3-O-glucoside, nicotiflorin, rutin
Phenolic compounds	Coumaric Gallic acid, 3,4-dihydroxybenzoic 4-hydroxybenzoic, and ferulic acid
PRICKLY PEAR FRUITS	
Minerals	K, Ca, Mg and Na
Vitamins	E, A, and C
Amino acids	Lysine, methionine, glutamine, and taurine
Organic acids	Maleic, malonic, succinic, tartaric, and oxalic
Pigments	Betaxanthins, betacyanins, and betalains
Fatty acids	Palmitic acid and linoleic acid
Flavonoids	Kaempferol, quercetin, and isorhamnetin
SEEDS	
Minerals	K and P. Lower proportions of Mg, Na and Ca
Sterols	β-sitosterol and campesterol
Fatty acids	Palmitic acid, oleic acid, and linoleic acid
Phenolic compounds	Ferulic acid, sinapoyl-diglucoside, synapoyl-glucose, and feruloyl-sucrose
PULP AND PEEL	
Minerals	K, Ca and Mg
Sterols	β-sitosterol and campesterol
Fatty acids	Palmitic acid, oleic acid, linoleic acid, stearic acids and linolenic acid
Carotenoids	Lutein, β-carotene, violaxanthin, lycopene, and zeaxanthin
Flavonoids	Quercetin, isorhamnetin, kaempferol, luteolin, and isorhamnetin glycosides
Phenolic compounds	Ferulic acid, sinapoyl-diglucoside, and feruloyl-sucrose isomer
FLOWERS	
Flavonoids	Kaempferol, quercetin, and isorhamnetin glycosides
Organic acids	Mainly gallic acid

B6, E, A, and C), minerals (mainly K and Ca), and betalains, such as betaxanthins (betanin and indicaxanthin) and betacyanins (betanidin, isobetanin, isobetanidine, and neobetanin) [18, 19, 31–33, 36, 37].

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) [38]. The mineral content of cactus pear fruit is essentially due to potassium, followed by calcium, magnesium and sodium. The bioactive compounds are represented by vitamin C, flavonoids, betalains (betanin and indicaxanthin), carotenoids and polyphenols, and are present in fruit peel and pulp. Betalains are water-soluble nitrogenous pigments and they are responsible for the red or yellow color of fruits, flowers, roots and leaves of plants belonging to the *Cactaceae* family [39]. Vitamin C is an essential nutrient for humans and other vitamins that provide high antioxidant activity and prevent against oxidative stress in humans [40]. 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 [41]. 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 kaempferol and isorhamnetin. 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 [42]. Polyphenols, among which resveratrol is commonly mentioned [43], are an important group of natural compounds found in plants and are 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 [44].

Various studies have shown the action of phytochemicals as substrates to activate different biochemical reactions that provide important health benefits. For that reason, they could be included in the definition of nutraceutical: "*Any non-toxic food extract supplement that has been scientifically proven to be beneficial to health both intreating and preventing diseases*" [31, 45, 46]. Different authors agree that the carotenoids are important compounds with great benefits for human health, related to the prevention and reduction of the development of some diseases, such as cardiovascular diseases, cancer and macular degeneration and that taurine (semi-essential amino acid) is involved in the modulation of the inflammatory response with potential antioxidant. As well as, that some plant sterols are incorporated into foods intended for human consumption to lower blood cholesterol levels [47, 48]. On the other hand, scientific evidence suggests that phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids), flavonoids, lignins and stilbenes have a high antioxidant potential that has been related in many health benefits, such as prevention of inflammation, cardiovascular dysregulation, and neurodegenerative diseases [47, 49]. In this same approach, it is known that flavonoids are a group of bioactive compounds that exhibit many effects in the protection of the body, and their regular consumption is associated with reduced risk of several chronic diseases (especially, for its antioxidant, antiviral and antibacterial capacities). Betalains are powerful radical eliminators in chemical systems and act as efficient antioxidants in several biological models, potentially useful as a strategy against intestinal inflammation [48–50]. Indicaxanthin ((2*S*)-2,3-dihydro-4-[2-[(2*S*)-2α-carboxy pyrrolidin-1yl]ethenyl] pyridine-2α,6-dicarboxylic acid), the yellow pigment characterizing the edible fruit of the cactus *Opuntia ficus-indica* (L. Mill), is a water-soluble alkaloid belonging to the class of betalain phytochemicals. It depicts the chemical structure of betalamic acid, is a dietary pigment from OFI fruit [51]. Extensive research has demonstrated that indicaxanthin has a variety of biological properties, including antioxidant [52] and anti-inflammatory [53] effects. A number of recent in vitro studies showed that indicaxanthin is a reducing and amphipathic molecule capable of penetrating cells and membranes and counteracting oxidative damage [1, 54]. Most recently, its chemopreventive and antitumor activities in vitro and in vivo has also been demonstrated [55–57]. In this context, opuntioid cacti reveal different mechanisms of action that can be interrelated and favor their biological effects.

Bioactives extraction techniques

Recently, Kadda et al. [58] described three different approaches for the extraction of bioactives from seeds of the fruit. Sampled fruits were harvested from Eastern region of Morocco, washed thoroughly with water to remove dust and spines, and then peeled; seeds were separated from the juice by passing through a sieve with a 2-mm screen, washed with distilled water, and dried at room temperature (25 °C), for 10 days [58]; some seeds were used for mechanical extraction, and others were reduced to a fine powder using a Taurus coffee grinder for the chemical and maceration extraction [58]. Three types of extractions were used, namely, chemical extraction, maceration and mechanical extraction. In the chemical extraction, seeds were crushed until obtaining a fine powder. Of this powder, 40 g is subjected to an extraction in a Soxhlet by 200 ml of n-hexane (99%) at a temperature of 60 °C for 7 h. The solvent was removed using a steam rotator at a temperature of 40 °C. The obtained oil was conserved in a refrigerator at a temperature of 4 °C [58]. With respect to maceration, which consists of letting a solid mass remain in a cold liquid to extract soluble compounds, the extracts were prepared from the seed powder using n-hexane 99% under stirring at room temperature for 2 h. The extracts were then filtered by a Büchner-type filter, and the filtrate was then filtered through a crucible with a porosity of 4 µm. The solvent was removed from the filtrate by a steam rotator to recover the oils which were then preserved at 4 °C until further use [58]. The mechanical extraction under hot press (120 °C), which is a biological method used to extract oil from the seeds, these latter were placed between permeable barriers by increasing the mechanical pressure thus reducing the volume available for the seeds. In general, regardless of the seeds used, the higher the pressure, the higher the oil extraction efficiency. In an oil press brand, the prickly pear seeds were pressed to obtain the oil at a temperature of 120 °C, filtered and preserved at 4 °C until further use [58].

To obtain oil from the seeds of *Opuntia ficus-indica* L., Khémiri et al. [59] described the harvesting of mature prickly pears from the village of Zelfen, Kasserine, central Tunisia. This region is known for its hard semi-arid climate conditions. The fruits were peeled manually. The seeds were then isolated mechanically, washed with potable water, and dried. The oil extraction was carried out mechanically without any chemical treatment, using an oil press machine. After filtration, the first cold-pressed OFI seed oil was stored in anti-UV hermetic bottles, in order to preserve the alteration of its components [59].

Allegra et al. [57] described the isolation of indicaxanthin from OFI fruits. Briefly, the fruits were peeled and finely chopped, the pulp was separated from the seeds and weighed, and pulp samples were homogenized and centrifuged at 3000×*g* for 10 min. The supernatant was recovered while the pellet was extracted with distilled water and centrifuged again. The combined supernatants were subjected to cryodesiccation, and the phytochemical, in the resulting aqueous extract, was separated by size exclusion chromatography. Fractions containing the pigment were subjected to cryodesiccation, followed by solid-phase extraction. The eluate was subjected to rotary evaporation to remove methanol and the residue dissolved in phosphate-buffered saline, and stored at − 80 °C [57].

Fresh samples of OFI cladodes were collected from Adigrat district, Eastern zone of Tigrai Region, Northern Ethiopia [60]. The collected samples were washed thoroughly with tap water and rinsed with distilled water. The cleaned samples were cut into small pieces and dehydrated at 60ºC for two days. Dried samples were grinded in a domestic grinder and the powders were sieved at 1 mm. The obtained fine powders were stored in dark plastic bags at room temperature [60]. For the extraction and screening of phytochemicals, each fine powder samples of cladodes were mixed with ethanol, methanol and chloroform in a 1:4 ratio (w/v) ratio in different Erlenmeyer flasks and the flasks were covered with aluminum foil. The mixtures were refluxed at 60 °C for 7 h. The extracts were filtered using Whatman filter paper no. 4. The solvents were removed using a rotary evaporator, using a temperature below 60 °C [60].

Amrane-Abider et al. [61] described the collection of fruit samples of OFI from the area of the Talendjaste village (Bejaia, Algeria), from mature plants (orange-red color). Samples were washed with distilled water and peeled manually. The peels were lyophilized. The dry OFI flowers (post following stage, pale yellow color) were collected from the same place. Both peels and flowers were ground, then sieved, and after that, the powder was stored at 4 °C in airtight bags until further use. Aqueous OFI peel and flower extracts were prepared as follows: After infusion of the powder for 10 min in boiling water, the obtained solution was filtered [61].

Biopharmaceutical applications of *Opuntia ficus-indica*

Table 2 gives an overview of the main biomedical and biopharmaceutical applications of *Opuntia ficus-indica* extracts and its bioactives.

Antibacterial activity

The discovery and use of new antimicrobial agents, mostly from plants, can be an alternative to help overcome antimicrobial resistance, one of the most serious health problems. Ramírez-Moreno et al. [63] tested the antimicrobial activity of the OFI seeds oil against *Candida albicans*, *Escherichia coli* O58: H21, *Escherichia coli* O157: H7, *Staphylococcus aureus*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae* and *Salmonella typhimurium*. The results showed that the oil extracts have high antimicrobial activity against Gram-positive and Gram-negative bacteria. In another study, described by Welegerima and Zemene [64], the antimicrobial potential of extracts from OFI was studied. The peel extracts showed greater antimicrobial activity against Gram-positive bacteria than Gram-negative bacteria. The results obtained also demonstrated a greater antimicrobial activity of the prickly pear peel against *S. typhimurium* (S456), *Bacillus subtilis* (B2836) and *Streptococcus pneumoniae* (ATCC63) compared to tetracycline and vancomycin. Cladodes extracts also have antimicrobial activity. According to the results obtained by Welegerima et al. [60], cladodes extracts have antibacterial activity against both Gram-positive (*B. subtilis* and *S. pneumoniae*) and Gram-negative bacteria (*E. coli* and *S. typhimurium*).

Table 2 Main biomedical and biopharmaceutical applications of *Opuntia ficus-indica* extracts and its bioactives

Biological activities	Type of extract	Results (in vitro/in vivo)	References
Antibacterial	Oil extract	Antimicrobial activity against Gram-positive and Gram-negative bacteria	[60, 62–64]
	Cladode extract	Antibacterial activity against Gram-positive (*B. subtilis* and *S. pneumoniae*) and Gram-negative bacteria (*E. coli* and *S. typhimurium*)	
	Cladode	Antimicrobial activity against *Escherichia coli* MBC = 4 mg/mL and *Staphylococcus aureus* MBC = 1 mg/mL;	
Antiviral	Cladode	Antiviral activity against SARS-CoV-2 related to the presence of the chiral phytochemical astragalin; Antiviral activity against *Cucumber mosaic* virus due to the presence of antiviral proteins Opuntin A and Opuntin B	[22, 65]
Antidiabetic, and antihypertensive	Cladode	Glucose lowering effects in alloxan-induced diabetic rats;	[66, 67]
	Cladode extract	Diuretic effect on rats;	
	Cladode extract	Diuretic and hypotensive effect on normotensive rabbits without deterioration in renal function test	
Anti-inflammatory and antidiabetic	Indicaxanthin from Cactus Pear Fruit	Anti-Inflammatory and antidiabetic activity in mice (male) High-fat diet (HFD)-induced obesity (metabolic syndrome model)	[51]
Anti-proliferative	Indicaxanthin from Cactus Pear Fruit	Anti-proliferative activity in human tumor cells	[68]
Anticancer	Seed oil	Apoptosis in primer colon adenocarcionoma cell lines	[69]
Anticancer	Plant extracts	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	[70, 71]
Antioxidant, neuroprotective and hepatoprotective	Peels and Flowers	Antioxidant activity was evaluated using different assays (DPPH, RP, HPSA, ORAC, TEAC, LOX-FL); Reduction in hepatic damage by alcoholic oxidative stress related to the presence of (+)-taxifolin in rat hepatocytes	[61, 72, 73]
	Fruit extract		
Action on digestive disturbances	Seeds aqueous extract; Mature Cactus pear juice; Green Cactus pear juice	Antidiarrheal activity in rat;	[74, 75]
		Increase in gastrointestinal transit (presence of few tannins) in rat;	
		Decrease in gastrointestinal transit (presence of more tannins) in rat	
Anti-inflammatory and antiphotoaging agent	Opuntiol isolated	UVA radiation-mediated inflammation and skin photoaging in mice. The animals were shaved and exposed to UVA rays (dose of 10 J/cm^2/day) for 10 days	[76]

The antimicrobial activity of OFI against gram-positive and gram-negative bacteria and biofilms has already been reviewed. Sánchez et al. [62] described the antimicrobial activity of OFI cladodes against *Escherichia coli* and *Staphylococcus aureus* with a minimum bactericidal concentration (MBC) of 4 mg/mL and 1 mg/mL, respectively [62]. Recently, fruit peel has been studied for tis antipeneumonia activity. The authors demonstrated that the valuable constituents contained in the unused waste from OFI fruits have beneficial potential against pneumonia pathogens [77].

Antiviral activity

The antiviral activity of OFI has been described in the literature [78, 79]. 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 [65]. The same authors recently demonstrated that these proteins exhibit ribonuclease activity [80]. 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 [65], thus underlying the importance of chirality in pharmacological activities [81, 82]. The ethanol extract of OFI was found to exhibit antiviral activity against *Peste des Petits* ruminant virus, an enveloped virus with RNA as its genetic material and belongs to the genus *Morbillivirus* [83].

Antidiabetic, antiobesity and antihypertensive activities

The protective effect of OFI in diabetes has been demonstrated [66]. 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 [84]. 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 [85].

Terzo et al. [51] described a study, in mice, that indicaxanthin extracted from OFI fruits, that induced beneficial effects on glucose dysmetabolism. In fact, the indicaxanthin-treated HFD mice showed fasting glycaemia values that were significantly lower than those of HFD mice. Moreover, they showed improved glycaemic control, as indicated by the reduction in blood glucose levels during the i.p. glucose tolerance test higher insulin sensitivity as suggested by the insulin tolerance test and lower plasma insulin concentration in comparison with untreated HFD mice.

Héliès-Toussaint et al. [86] successfully reported anti-adipogenic effects of *Opuntia* cladode powders in an in vitro cellular model for adipocyte differentiation and an in vivo HFD-induced obesity rodent model, highlighting their potential use as dietary supplement for the management of obese patients. Opuntia callus was also studied with respect to its metabolites and their anti-adipogenic activities [87]. Authors identified 3,5-Di-O-galloylshikimic acid as the major compound, followed by gallic acid and epicathequin derivates. The adipogenic effects were attributed to the capacity to reduce lipid accumulation in 3T3 cells, during adipocyte differentiation. More recently, Sirotkin [88] 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 as highlighted by Corona-Cervantes et al. [26].

The fruit infusion shows diuretic and anti-uric activity [67]. 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 [67]. 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 [67].

Anti-proliferative and anticancer activities

Because cancer is seen as a disorder related to oxidative stress, phytochemicals with antioxidative capacity and a supposedly favourable side effect profile, have been the subject of research to prevent, counteract and treat this disease [89, 90]. Several reports show the benefit of indicaxanthin, a betalain phytochemical of the OFI, 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 [57]. Chemopreventive and pro-apoptotic activities and anti-proliferative effects of indicaxanthin were documented against several cell lines of different cancers. Apart from individual inhibitory effects on cancer cell growth, phytochemicals may exert synergistic effects with other phytochemicals or anticancer drugs [91]. Recent studies in HeLa cells [68] provide further information on the anti-proliferative effect of indicaxantin and suggest its eventual relevance to enhance chemosensitivity of cisplatin (CDDP). Remarkably, when cells were submitted to a combination regimen of indicaxanthin and CDDP, the Combination Index analysis [68] provided clear evidence of synergism. Moreover, the pre-treatment of HeLa cells with concentrations of indicaxanthin of nutritional relevance [68], which were ineffective in modifying cell viability per se, potentiated CDDP activity significantly.

OFI seed oil may have an anticancer effect on primer colon adenocarcinoma (Colo-320) cell lines by inducing apoptosis [69]. I*n vitro* antiproliferative activity of extracts of OFI has been demonstrated against PC3 prostate and mammary MCF-7 cell lines [92]. 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 [71]. It also shows antiproliferative activity against KB oral carcinoma cells [70]. 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 [93].

These findings support the assumption that OFI extracts have a strong potential to be used as the source of naturally found bioactive compounds that can provide a platform for cancer drugs development. A review by Tomczyk et al. [94] reported that OFI inhibited cancer cell growth in an in vivo model of mice ovarian cell culture [94]. The linoleic acid content of OFI may also possess further in vitro anticancer properties owing to the subsequent inhibition against colon cancer metastatic cells [33].

Hfaiedh et al. [95] showed that rats orally treated with 100 mg/kg cladodes for 40 days decreased lipid peroxidation and increased levels of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase). The researchers concluded that addition of OFI might reduce the risk of developing chronic diseases, including cancer, particularly testicular cancers [95].

Antioxidant, neuroprotective and hepatoprotective activity

Neuroprotective and antioxidant effects of OFI have been extensively studied. 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$^{\cdot}$), reducing power (RP), and hydrogen peroxide scavenging activity (HPSA). They also showed antiacetylcholinesterase activity that was higher in flowers than in peel teas [61]. The in vitro antioxidant capacity of OFI 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 [72]. OFI is also considered a plant with a hepatoprotective capacity [96]. 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 [35].

The antioxidant actions attributed toOFI fruit can be due to the presence of several compounds, namely vitamin C, carotenoids, but also polyphenols and flavonoid compounds like quercetin, kaempferol and isorhamnetin [97, 98]. Despite some differences within the composition of different cactus structures, it is possible to find some similarities in phytochemicals composition. Boutakiout et al. [99] have suggested that OFI cladodes are a good source of natural antioxidant compounds. The authors evaluated antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\cdot}$), 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and ferric reducing antioxidant power (FRAP) assays of OFI cladodes. The results obtained varied from 1.78 to 4.10 µmol Trolox equivalents/mL for DPPH$^{\cdot}$, 12.78 to 23.10 µmol Trolox equivalents/mL for ABTS and 1.74 to 3.33 µmol Trolox equivalents/mL for FRAP. The experimental study conducted by Saad et al. [100] has shown that the OFI cladode extract (100 mg/kg body weight) was able to reduce the oxidative lithium-induced damage through the increase in antioxidant enzyme levels (superoxide dismutase, catalase, and glutathione peroxidase). This effect is probably associated with the capacity of this extract to reduce the lipid peroxidation level in membrane cells by scavenging free radicals [100]. Moreover, the research conducted by Saad et al. [100] also demonstrates that cladode extract was able to reactivate the erythropoiesis mechanism and thus enhance the production of erythropoietin.

Action on digestive disturbances

OFI showed different activities against 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 antidiarrheal activity, a notable intestinal fluid accumulation decline and electrolyte concentrations reestablishment [74]. 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 disturbances [75].

The OFI 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 OFI 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 OFI fruit juice was demonstrated to be decreased [75].

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 [59]. 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 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) [101].

Anti-inflammatory and antiphotoaging properties

The anti-inflammatory activity of OFI has been known for many years [102]. Studies on OFI determined that this activity seems to be related to flavonoids [103], particularly to isorhamnetin glycosides [104, 105] and β-sitosterol [106], or to indicaxanthin [107]. 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 break-downs in UVA radiation-exposed mouse skin by inhibiting inflammatory responses, MAPK activation, and degradation of matrix collagen molecules [76].

Other pharmaceutical applications

OFI is commonly used as animal fodder due to their nutritional properties, such as the moderate content of sugars, starch, ether extract, crude protein, amino acids, fiber, and for providing a good amount of the animal requirements for vitamins and calcium, representing a better feed for ruminants than commercial feeds [108]. In rabbits fed with diets with 50% of CPP, giblets, liver and heart were heavier, and abdominal fat, triglycerides and LDL cholesterol were reduced, while the concentration of HDL cholesterol increased [109]. Adding a 15% of CPP to the traditional corn diets for commercial Cobb chicken, the weight gain improves in 5.78%, as well as the total protein and globulin in blood serum, resulting in superior nutritional status, greater daily weight gain, and better sensorial characteristics of the meat, including taste, colour, odor, texture, and general acceptability [110]. Some studies showed that supplementing the feeding of goats with cladodes and fruit peels may be an important resource to reduce their water intake, without detrimental effects on digestion, growth and meat quality [111, 112].

Concerning insecticidal activity, prickly pear peel waste has shown larvicidal activity as well as a decrease in the fecundity and hatchability of the *C. pipiens* mosquito [113]; however, more studies are needed to assess the antimicrobial activity of CPP extracts.

Synthetic colorants have been used in different types of industries because they present good stability and are cheap. However, the trend for using natural colorants is increasing, and the market derived from natural sources such as fruits, vegetables, insects or minerals represents a promising industry [114]. The peels of the cactus pear, mainly the red ones, are an important source of betanins, one of the most valued red natural colorants. These pigments are of great importance in the industry because of their ecological value and non-toxicity and are considered a permitted colorant for foods (USDA) [115]. Cactus pear by-products can be used in a more profitable way, by extracting the colorants before being used for animal feed [116], either using solvents, or novel clean technologies.

Other applications that have been described for OFI could be used in the phytoremediation of soils contaminated with heavy metals [117, 118] and OFI cladodes could be used to produce biofuels, specifically bioethanol and biogas [119].

Conclusions

The most abundant plants of the *Cactaceae* family belong to the genus *Opuntia* spp. OFI is the most representative of this family. 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. Although modern medicine is available in most countries for the control and treatment of many diseases, phytomedicine continues being popularly used in different populations for historical, cultural reasons, easy access, low cost, diversity, and especially, a relative lower quantity of adverse effects. This review demonstrates the beneficial properties of the different vegetative parts of *Opuntia ficus-indica*. For this reason, scientific research on this plant genus (known as succulents, due to their ability to generate biomass by storing water in one or more of their organs) has deepened and may continue to increase, in order to better understand its nutritional and therapeutic properties. 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 ongoing to explore this ancient plant's additional benefits and promising properties.

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Declarations

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