

# *Opuntia dillenii*: A Forgotten Plant with Promising Pharmacological Properties

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## Key Words

*Opuntia dillenii*, anti-oxidant, immuno-modulation, neuro-protection, pharmacological activity, anti-tumor

## List of abbreviation

ALT: Alanine transaminase

AST: Aspartate transaminase

DDPH: 2,2-diphenyl-1-picrylhydrazyl

GR: glucocorticoid receptor

GSH: Glutathione

GSH-PX: Glutathione peroxidase

GST: Glutathione S-transferases

Ip: intraperitoneal

MDA: Malondialdehyde

*Opuntia dillenii* (OD)

ODT: OD tablet

RSM: Response surface methodology

## Abstract

Generative and vegetative parts of the cactuses have had a long-lasting position in folk medicine and their effects could partly be confirmed in scientific experiments. Nowadays, the cactus, fruits, and cladodes are the focus of many studies because of their desirable properties. Therefore, the summarized reports of valu-

able properties of medicinal plants may be a good way to familiarize researches with a new source of drugs with lower side effects and higher efficacy.

*Opuntia dillenii*, a well-known member of the Cactaceae family, is used as a medicinal plant in various countries and grows in the desert, semi-desert, tropical and sub-tropical areas. It shows diverse pharmacological activities such as: antioxidant, anti-inflammatory, anti-tumor, neuroprotective, hepatoprotective, hypotensive etc. *OD* fruit also possesses valuable constituents for instance: betalains, ascorbic acid, total phenol, protein as well as essential elements which suggest the significant potential of this plant as a complementary therapy against several pathological conditions. This review describes experimental evidence about pharmacological and therapeutic potential of *OD* in order to give the basis of its application in the prevention and treatment of some chronic diseases. More studies on *OD* can help better understanding of its pharmacological mechanism of action to explain its traditional uses and to identify its potential new therapeutic applications.

## 1. Introduction

From ancient times, in search for rescue from diseases, the people are looking for drugs in natural environments. The onset of the medicinal plants' use was instinctive and there was not enough information about the reasons for the illnesses and how plants could be utilized as a cure [1]. The genesis of iatrochemistry in

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the 16th century was the start of using plants as a source for treatment and prophylaxis of diseases [2]. Nowadays, it is reported that about 2000 medicinal plant groups exist throughout the world, each one has its unique clinical value or chemical compositions [3, 4]. Plants have received great attention in developed countries as valuable compounds with acceptable efficacy and safety in treating different diseases. It has been reported that more than 3.3 billion people in the low-population countries use medicinal plant on a regular basis [5]. An estimation by the world health organization (WHO) showed that about 80% of African people rely on herbal medicines for the treatment of many diseases [6]. Nowadays many pieces of research have revealed side effects of chemical drugs and this made many people notice the medicinal plants chemical drugs. Developed side effects even may show up at their right dose as well as in combination with other drugs. Drugs adverse effects impress about 2 million patients in the United States annually and cause an approximately 100,000 deaths. In this regard, the exhibition of severe adverse effects made US Food and Drug Administration advisory panel to ban the popular pain relievers Percocet and Vicodin [7, 8]. In this context, it made researches all around the world to conduct various researches in the topics of medicinal plants among these researches, review studies expressing the value and importance of specific herbal products play vital roles.

*Opuntia dillenii* (OD) a plant form Cactacea growing in dry and desert environments is a great medicinal herb, a shrub grows in desert and dry conditions with a height of

about 1 to 1.8 meters [24]. Additionally, OD has very beautiful flowers with amazing coloration due to betalain and possess important chemicals including betanin, polysaccharide composition of galactose and arabinose, 3-O-methyl quercetin, kaempferide, kaempferol, isorhamnetin, quercetin, beta-sitosterol, 4-ethoxy-6-hydroxymethyl-alpha-pyrone, opuntisterol, opuntisteroside, taraxerol, friedelin, methyl linoleate, 7-oxositosterol, 6- $\beta$ -hydroxystigmast-4-ene-3-one, daucosterol, eucomic acid, methyl eucomate and also with moisture, protein, brix, acidity, glucose, fructose, saccharose and minerals. The species OD, Nagphana, is not much explored while its protective effects have so far been reported including analgesic, anti-inflammatory [9], radical scavenging activity [10] and anti-spermatogenic effect [11] as well as especially known as an anti-diabetic and anti-inflammatory agent from past decades [12, 13]. Regarding the traditional uses, it has been suggested that the fruit of OD may be useful as a medication for gonorrhoea, whooping cough and constipation, as well as controlling the bile secretion, spasmodic cough and expectoration. Additionally, leaves of the plant have been applied as a medication for the wound and inflammation as well as a treatment for ophthalmic disorders [12, 14].

On this basis, the aim of the present study is to summarize the valid data on OD and its chemical composition and potential pharmacologic properties to have a better insight on the position of OD among various medicinal plants and its further potential application (Table 1).

**Table 1** Summarization of pharmacological properties of OD

Pharmacologic effect	Model	Measurements	Evidence
Anti-inflammation	carrageenan-induced paw edema in rats	Percentages of edema	Reduction of edema percentage based on the dose-related manner [9].
Anti-inflammation	carrageenan-induced paw edema in rats	Percentages of edema	The most anti-inflammatory effect for the flower extraction at a dose of 200 mg/kg [48].
Anti-inflammation	arachidonic acid(AA) and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) ear edema of mice- phospholipase A2 (PLA2)-induced mice paw edema Carrageenan and glycogen- induced peritonitis in rodents	leukotriene B4 (LTB4)- reactive oxygen species (ROS)- prostaglandin E2 (PGE2)-tumor necrosis factor (TNF- $\alpha$ ) interleukins (IL-1 $\beta$ IL- 6)	Reduction of AA and TPA induced ear punch to weigh in a dose-dependent manner- Attenuation of paw edema and peritonitis-reduction of PGE2, LTB4, ROS and cytokine levels (TNF- $\alpha$ , IL-1 $\beta$ IL -6) [26].
Immunomodulatory effect	Murine immunosuppressed by intraperitoneal injection of cyclophosphamide (Cy, ip).	Intraserous hemolysin IgM, IgG levels- the proliferation of splenocytes - the proportion of T lymphocyte subsets in peripheral blood- main component purified from OD polysaccharides on the lymphocytes in vitro	OD can potentially enhance the specific immune function of immunosuppressed mice and the proliferation of lymphocytes [86].
Antioxidant	DHPP assay	DPPH free radical scavenging activity	IC50 for scavenging activity on DPPH free radical was decreasing by the increment of OD extract purity [54].
Antioxidant	DHPP assay	DPPH free radical scavenging activity	DPPH radical scavenging activities of the 3,4-dihydroxy substituted flavonoids (such as quercetin) were stronger than those of the 4-hydroxyl substitutes (such as kaempferol) [56].
Antioxidant	DPPH test, hydroxyl radicals, and superoxide radical in vitro	DPPH, hydroxyl and superoxide radicals scavenging.	2-4 month-old OD had higher antioxidant activity than 5-10 month-old OD and a fraction isolated from OD (ODP-Ia) was superior to 5-10 month OD [57].

Pharmacologic effect	Model	Measurements	Evidence
Antioxidant	On the basis of the ability to scavenge the ABTS <sup>•</sup> radical in vitro Folin-Ciocalteu reaction	Measurement of ABTS <sup>•</sup> free radical And Folin-Ciocalteu reduction capacity (FCRC)	The antioxidant activity of extracts of OD fruit was based in the bottom order (crude extract (CE) > purified extract (PE) > red fraction (RF) > yellow fraction (YF) in concordance with the (FCRC) [31].
Antioxidant	Oxygen radical absorbance capacity (ORAC) assay	Measurement of the ability of antioxidant components in test materials to inhibit the decline in R-PE fluorescence induced by a peroxy radical generator R-PE fluorescence that is induced by a peroxy radical generator, AAPH.	The varieties with red-skin fruits ( <i>O. streptacantha</i> ) contained the most ascorbic acid and the yellow-skinned fruits ( <i>Opuntia stricta var. stricta</i> ) had the most carotenoids. Relation of antioxidant activity to their flavonoid, ascorbic acid and carotenoid contents [58].
Antioxidant	TEAC assay - Oxygen-radical absorbance capacity assay (ORAC) (Clinical trial)	Trolox equivalent antioxidant capacity (TEAC) assay as described by Miller, Rice-Evans, Davies, Gopinathan, and Milner [87]-Oxygen- radical absorbance capacity assay (ORAC) assay was based on the report by Cao, Sofic, and Prior [88] with a slight modification	Higher antioxidant capacity for betacyanin-free seeds of OD than extracts from peel and pulp with betacyanins [43].
Neuro-protective	Brain ischemia- reperfusion injury in rats-the oxidative stress-induced damage in PC12 cells	Neurological deficit score- infarct volume- neuronal loss in the cerebral cortex- protein synthesis of inducible nitric oxide synthase-cell viability- H <sub>2</sub> O <sub>2</sub> induced apoptosis-both intracellular and total accumulation of reactive oxygen species (ROS) production- Bax/ Bcl-2 mRNA ratio	Cactus polysaccharides (200 mg/kg) significantly decreased the neurological deficit score, reduced infarct volume, decreased neuronal loss in cerebral cortex, and also reduced the protein synthesis of iNOS- protection of PC12 cells against hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> ) destruction- elevation of cell viability, reduction of H <sub>2</sub> O <sub>2</sub> induced apoptosis decrement both intracellular and total accumulation of reactive oxygen species (ROS) production, upregulation of Bax/ Bcl-2 mRNA ratio[65].
Anti-diabetic effect	Normoglycemic and alloxan-induced diabetes rabbits	Plasma insulin levels blood glucose levels	Hypoglycemic effect of this plant partly due to reducing intestinal absorption of glucose [42].
Anti-diabetic effect	46 type 2 diabetes mellitus (DM) patients (clinical trial)	Observation of symptoms- determination of FBG, PBG and 24 hrs urinary sugar - glycosylated hemoglobin- fasting insulin (FINS), 2 hrs post-meal insulin (PINS) and glucagons (GC)- sensitivity of insulin (SI)- Serum B <sub>2</sub> micro-globulin (SB <sub>2</sub> - MG)-urinary B2 micro-globulin (U-B <sub>2</sub> -MG)- serum Tamm-Horsfall (S-THP) - urinary Tamm-Horsfall (U- THP)-serum endothelin (S-ET) and urinary endothelin (U-ET)- micro-albumin (MA)-α micro-globulin (α-MG)- transferrin (TRF) - IgG and plasma NO	Improve the glycometabolism of DM patients sufficiently and avoid the impairment of renal function in diabetic neuropathy [83].
Anti-diabetic effect	Streptozotocin (STZ)- induced diabetes in rats	Body weight gain%- blood glucose concentration liver glycogen content- lipid peroxide (MDA) level- total cholesterol (TC), triacylglycerols (TAG), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) high-density lipoprotein cholesterol (HDL-C)	Administration of OD juice to diabetic rats significantly improve lipid profile and body weight gain %, it also significantly reduced MDA levels and blood glucose [84].
Anti-diabetic effect	Streptozotocin (STZ)- induced diabetes in mice	Blood glucose	The results show that OD Haw. polysaccharides have hypoglycemic activity [89].
Analgesic	Hotplate and writhing test in rat and mice	Number of writhing movements and Reaction time	The increment of the reaction time of rats from the dose 100 mg/kg and reduction of writhing movements in a dose- dependent manner [9].
Analgesic	Electric current test in rats	Volts needed as a noxious stimuli	Definite analgesic action at a dose of 200 mg/kg of flower extract [48].

Pharmacologic effect	Model	Measurements	Evidence
Anti-tumor effect	Lung squamous carcinoma cells (sk- mes-1)	Cell proliferation assay- Morphology test- Cell cycle and apoptosis analysis- Western- blotting analysis- Annexin-V assay	Prevention of SK-MES-1 cells growth and induction of S phase arrest. Cactus polysaccharides cause apoptosis in SK-MES-1 cells determined by Annexin-V assay. cactus polysaccharides induced growth arrest and apoptosis may be due to the increase of P53 and phosphatase and tensin homolog deleted on chromosome ten (PTEN) protein [90].
Hypotensive activity	Sprague-Dawley rats - NMRI mice	Mean Arterial Blood Pressure (MABP)- Toxicology of extract indicated by the change in the physical behavior or motor activity of animals and appearance of the animal- Tissue Analysis and Histopathology- Serum Cholesterol, Glucose, Bilirubin, and Total Protein Levels	Administration of methanolic extract of <i>OD</i> and <i>opuntioside-1</i> showed a decrease in the MABP of rats by three different routes (intravenous, intraperitoneal, and oral) of administration is significant [76].
In-Vitro antimicrobial	Plate hole diffusion- Agar well diffusion- Saubouraud dextrose agar medium (SDA)- cup plate method	Determine the growth inhibition of bacteria- Anti-tubercular assay using Microplate Alamar Blue Assay (MABA) with the suspension of Mycobacterium tuberculosis H37Rv strain	Among the various microorganisms, the aqueous methanolic extract was more active against <i>Micrococcus leuteum</i> , <i>Proteus mirabilis</i> . In the antifungal activity of the aqueous methanolic extract shows positive results for all fungus. The antitubercular activities were compared with standard drug Rifampicin. The aqueous methanolic extract was having more percentage inhibition when compared to other extracts [91].
In-Vitro antimicrobial	antimicrobial activities of fungi isolated from surface of <i>OD</i> evaluated against three Gram-positive bacteria, <i>Bacillus subtilis</i> (UBC 344), <i>Staphylococcus aureus</i> (ATCC 43300) and MRSA (ATCC 33591), two Gram- negative bacteria, <i>E. coli</i> (UBC 8161), <i>P. aeruginosa</i> (ATCC 27853) and the pathogenic fungus <i>C. albicans</i> (ATCC 90028).	ESIMS and NMR spectroscopic. minimum inhibitory concentrations (MICs)	Eight endophytic fungi obtained from <i>OD</i> surface and all except one exhibited antibacterial activities against at least one of the test bacteria. All extracts were inactive against <i>C. albicans</i> . The most bio-active fungus was <i>Fusarium</i> sp. [79]
In-Vitro antimicrobial	Extracts from the dried stem of <i>Opuntia</i> evaluated for antimicrobial activities against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , and <i>Salmonella typhi</i> by extraction in non-polar (petroleum ether and chloroform) and polar solvents (methanol and water).	An agar-well diffusion method was used to determinate the antibacterial activities.	<i>Bacillus subtilis</i> and <i>Staphylococcus aureus</i> were susceptible to all extracts of <i>Opuntia dillenii</i> . Ether and chloroform extracts of <i>O.dillenii</i> exhibited antimicrobial activity against <i>Escherichia coli</i> . <i>Salmonella typhi</i> was resistant to all of <i>O.dillenii</i> extracts. [80]
Hepatoprotective	CCl4-induced liver injury in mice	Serum ALT and AST activities, the content of liver GSH and GR, GST, GSH-Px activities levels, histopathological evaluations	<i>OD</i> polysaccharides can protect mice against CCl4 induced hepatotoxicity possibly due to its antioxidative capability of strengthening the GSH system [75].
Hepatoprotective	Cadmium-induced liver injury in mice	Hepato- histopathological indicator	Alteration of hepatic- histopathological changes after cadmium treatment reveals the curative role of <i>OD</i> in liver injury [74].

## 2. Material and Method

This review is included available data reporting in the literature about morphology, phytochemistry, ethnopharmacological applications and pharmacology of *OD* until December 11, 2018. For collection of data, scientific databases consisting of PubMed, Science Direct, Scopus, Web of Science, Scirus and Google Scholar were used. The search keywords were *Opuntia*, *Opuntia dillenii* (*OD*), pharmacological properties, antioxidant, anti-inflammatory, neuroprotective, hepato-protective, anti-cancer, Immuno-modulatory, hypotensive, anti-diabetic, chemical composition and their mixture. We also explored the therapeutic potential of *OD* in the field of ethnopharmacology. Finally, about 142 articles from 1972-2018 were found that 91 cases of them were selected for our study. In our study, the inclusion criteria were studies in English, accessibility to full text and articles mentioned pharmacological properties of *OD* and other genera of *Opuntia*. The articles that were not in English or the full text was not available, were excluded.

### 2.1. *Opuntia dillenii* (*OD*)



**Figure 1** *OD* Photograph by Sheldon Navie

*OD* is a member of the Cactaceae family (Figure 1), which is found in all temperature zones and has been used as an ornamental plant [12, 15]. The Cactaceae consists of 130 genera and 1500 species, which have remained largely unexplored for their therapeutic potency [12, 16]. *OD* cactus has a specific name: *OD* (Ker-gawl) Haw. and also called as Australian pest pear, common prickly pear, Dillen's

prickly pear, Eltham Indian fig, erect prickly pear, pipstem prickly pear, Gayndah pear, sweet prickly-pear, spiny pest-pear, spiny pest pear, sour prickly pear, sweet prickly pear and prickly pear [17]. It is a plant growing in deserts and semi-desert areas, including tropical and sub-tropical areas like south-eastern parts of North America and east coast of Mexico, the Bermudas, the West Indies and from the north of South America as well, the Gulf Coast of Texas and the south-eastern beaches of Brazil [18-21]. Moreover, this plant is found in around the Mediterranean [16], the Canary Islands, Madagascar and Mauritius, North Yemen, India, Pakistan, the south-eastern parts of Asia and Australia [9, 11, 19, 22-27].

### 2.2. Chemical composition

The *betalains* a natural pigment with pharmacological properties such as antioxidant, anti-cancer, anti-lipidemic and antimicrobial activity are the most constitute of *OD*. Their biosynthesis is based on the ability of plants to provide betalamic acid which condenses with cyclodopa or amino acids in non-enzymatic reactions [28-30]. The consumption of *OD* fruits represents an important contribution to the intakes of fiber, ascorbic acid, Mn, Cr and total phenolics which makes it a great antioxidant and also a powerful complementary diet (Table 2) [31].

#### 2.2.1. Cladode

Kalegowda P *et al.* showed that mucilage extracted from cladodes of *OD* (Ker-Gawl) Haw in aqueous medium yields about 6.2%. The neutral sugar composition consisted of arabinose (38.80%), rhamnose (15.70%), galactose (33.00%), xylose (5.10%) and glucose (5.10%) [32, 33]. Furthermore, some investigations show the isolation of two new  $\alpha$ -pyrones, called *opuntioside II* and *opuntioside III*, from the cladode and stem of *OD* extract with about six known compounds together. The structures of these new compounds were determined based on the chemical and physicochemical researches [34].

#### 2.2.2. Fruit

In a study conducted by Elena Díaz-Medina *et al.*, differences in chemical compositions between the fruit of *OD* and *Opuntia ficus indica* were evaluated. Results showed *OD* had higher contents of fiber, fat, ash, acidity, ascorbic acid, total phenolics, Na, Ca, Mg, Mn and Cr ( $p < 0.05$ ) and lower values of °Brix, proteins, pH, K, Fe, Zn and Ni [35]. These studies were not the only researches evaluating chemical composition of this plant. Other studies also had revealed the chemical composition (protein, Brix, moisture, acidity, saccharose, glucose, fructose and minerals), the physical properties (Linear dimensions, density, mass, shrinkage and porosity) and equilibrium properties (sorption isotherms, enthalpy and entropy) of *OD* fruit. This fruit is a valuable resource for water content, minerals, and acidity. Investigation on another plant of this family named prickly pear has revealed a value of total soluble solids (12-17%), acidity (0.03-0.12%), pH (6.0-6.6),

**Table 2** Chemical composition of *O.dillenii*

plant	part	Chemical composition
<i>Opuntia dillenii</i>	fruit	fiber, fat, ash, acidity, ascorbic acid, total phenolics, Na, Ca, Mg, Mn and Cr, °Brix, proteins, K, Fe, Zn, and Ni. saccharose, glucose, fructose and minerals, water content. <sup>14</sup> C-labeled betanidin an indole carboxylic acid
	Seed	calcium, phosphorus, potassium, magnesium, sodium and zinc.fatty acids such as linoleic acid, Palmitic acid.
	Cladode	neutral sugar composition consisted of arabinose, rhamnase, galactose, xylose, and glucose, two new $\alpha$ -pyrones, called opuntioside II and opuntioside III.
	Stem	novel C <sub>29</sub> -5 $\beta$ -sterols, opuntisterol [(24R)-24-ethyl-5 $\beta$ -cholest-9-ene- $\beta$ ,12 $\alpha$ -diol] and opuntisteroside [(24R)-24-ethyl-6 $\beta$ -[( $\beta$ - d-glucopyranosyl)oxy]-5 $\beta$ -cholest-9-ene-12 $\alpha$ -ol], $\beta$ -sitosterol, taraxerol, friedelin, methyl linoleate, 7-oxositosterol, 6 $\beta$ - hydroxystigmast-4-ene-3-one, daucosterol, methyl eucomate and eucomic acid, 3-O-methyl quercetin, kaempferol, kaempferide, quercetin, isorhamnetin and $\beta$ -sitosterol, 4- ethoxyl-6-hydroxymethyl- $\alpha$ -pyrone Kaempferol, kaempferide and 3-O-methyl quercetin, methyl linoleate, 7- oxositosterol, 6 $\beta$ -hydroxystigmast-4-ene-3-one and eucomic acid , opuntioside I, 4-ethoxyl-6-hydroxymethyl- $\alpha$ -pyrone, and kaempferol 7-O- $\beta$ -glucopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D- glucopyranoside.

ascorbic acid contents (20-40 mg/100 g fresh weight) nutritional values of energy (172 kJ), vitamin C (14 mg), glucose (7.8 g), fibre (1.8 g), protein (0.7 g), fats (0.5 g), potassium (220 mg), magnesium (85 mg), calcium (56 mg) and phosphorous (24 mg) for 100 g eatable portion. This plant is used in dehydrated areas as an edible product too [44-46]. its revealed that <sup>14</sup>C-labelled betanidin an indole carboxylic acid is a compound found in the fruits of *OD* [36].

### 2.2.3. Seed

M. Ramdani *et al.* reported that the minerals of *OD* dry seeds consist of: calcium at 408.28; phosphorus at 970.15; potassium at 201.96; magnesium at 240.30; sodium at 18.18 and zinc at 78.26 mg / 100 g dry seeds. The seed oil of *OD* mainly contains fatty acids such as linoleic acid: 79.83%, Palmitic acid: 13.52% [37].

### 2.2.4. Stem

The previous investigations also show two novel C<sub>29</sub>-5 $\beta$ -sterols, opuntisterol[(24R)-24-ethyl-5 $\beta$ -cholest-9-ene-6 $\beta$ , 12 $\alpha$ -diol] and opuntisteroside [(24R)-24-ethyl 6 $\beta$ -[( $\beta$ -d-glucopyranosyl)oxy]-5 $\beta$ -cholest-9-ene-12 $\alpha$ -ol], together with nine known compounds,  $\beta$ -sitosterol, taraxerol, friedelin, methyl linoleate, 7-oxositosterol, 6 $\beta$ -hydroxystigmast-4-ene-3-one, daucosterol, methyl eucomate and eucomic acid, were isolated from the stems of *OD* collected in Guizhou Province, China [20].

Qiu Yingkun *et al.* could isolate six compounds from *OD*-stems called 3-O-methyl quercetin, kaempferol, kaempferide, quercetin, isorhamnetin and  $\beta$ -sitosterol on the basis of the chemical evidence and spectral analysis. In another study, a new compound named 4-ethoxy-6-hydroxymethyl- $\alpha$ -pyrone was isolated from the 80% ethanolic extract of the stems of this plant [38]. Kaemp-

ferol, kaempferide and 3-O-methyl quercetin were isolated for the first time from *OD* stems [39]. Some studies demonstrated that compounds like methyl linoleate, 7-oxositosterol, 6 $\beta$ -hydroxystigmast-4-ene-3-one and eucomic acid were isolated from the stems of *OD* for the first time [40, 41]. Furthermore, investigations obtained three new compounds, opuntioside I, 4-ethoxy-6-hydroxymethyl- $\alpha$ -pyrone and kaempferol 7-O- $\beta$ -D- glucopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranoside, from the stem extract of *OD*. The structures of the new compounds were determined on the basis of chemical and physicochemical evidence [10].

## 2.3. Medicinal Uses

There is considerable evidence of using this plant as medicinal plant in various countries throughout the world, including *India* [11], *Canary Islands* [9, 42], *Taiwan* [43], *China* [10] where this plant has drawn great attention and some healthy drinks are provided from its extraction too [44-46].

## 2.4. Pharmacological properties

### 2.4.1. Immuno-modulatory, Anti-inflammatory activities and analgesic activities

Many studies have indicated the analgesic and anti-inflammatory effects of the genus *Opuntia* in many various extract types like fruit extract, lyophilized cladodes or the phytosterols from fruit and stem extracts [47]. It has been reported that this plant presents anti-inflammatory effects. Lyophilized aqueous extract of the fruits of the plant, used in *Canarian* traditional medicine for gastrointestinal and bronchial troubles, was evaluated for analgesic and anti-inflammatory effects in rats and mice. The *OD* extract

(100-400 mg/kg, i.p.) inhibited, in a dose-related way, carrageenan-induced paw edema in rats. A dose-dependent action was obtained against chemical (writhing test) and thermic (hot plate test) stimuli, respectively, with doses of 50 and 100 mg/kg [9]. In another study, evaluation of the anti-inflammatory and analgesic effects of the alcoholic extracts of flowers, fruits and stems of *OD* using carrageenan-induced rat paw edema and electrical current tests showed the most anti-inflammatory effect at the dose of 200 mg/kg of flower extract. Bioassay-guided fractionation of this extract by vacuum liquid chromatography (VLC) followed by Sephadex and paper chromatography showed three flavonoid glycosides i.e. kaempferol 3-O- $\alpha$ -arabinoside, isorhamnetin-3-O-glucoside and isorhamnetin-3-O-rutinoside [48]. Siddiqui *et al.* showed the anti-inflammatory effect of *OD* cladode methanol extracts using inhibition of arachidonic acid metabolites and cytokines. Their report also described the anti-inflammatory activity of *opuntiol* and *opuntioside* for the first time [26]. The other members of this genus such as *Opuntia ficus indica* and *Opuntia humifusa* have also been reported to exhibit anti-inflammatory effects [49-53]. Investigation of specific modulation of the immune system by *OD* polysaccharides in a murine model immunosuppressed by intraperitoneal injection of cyclophosphamide (ip) showed that this plant can potentially enhance the specific immune function of immunosuppressed mice as well as the proliferation of lymphocytes in vitro [78].

#### 2.4.2. Antioxidant activity

Yang Q *et al.* evaluated the antioxidant activity of crude polysaccharides from *OD* by DPPH assay used response surface methodology (RSM) to optimize the extraction. Their study revealed *OD* crude polysaccharides had a good antioxidant activity [54].  $\beta$ -Sitosterol isolated from *OD* as the active anti-inflammatory compound seems to be relatively weaker compared with that of hydrocortisone [25, 55].

The aqueous ethanolic extract from the fresh stems of *OD* has potent radical scavenging activity. In this study, three new compounds isolated from *OD* called *opuntioside* I, 4-ethoxyl-6-hydroxymethyl- $\alpha$ -pyrone and kaempferol 7-O- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranoside, were evaluated based on the chemical and physicochemical evidence. The radical scavenging effects of principal compounds were examined too [56]. Li H *et al.*, evaluated the antioxidant effect of polysaccharides isolated from *OD* using DPPH test, hydroxyl radicals and superoxide radical in vitro. Their study showed these acidic polysaccharides demonstrated good antioxidant activity [57]. A purification and fractionation of *OD* extract isolated several *betalains* and *polyphenol*. This process followed by betalainic and phenolic characterization revealed that this plant was a valuable source of bioactive compounds, with a high amount of total betacyanins (16.63 mg betanin/100 g fresh fruit) and betaxanthins (7.55 mg indicaxanthin/100 g fresh fruit) with elevated antioxidant activity [31]. The antioxidant activities in extracts obtained from four cacti (*Opuntia* species) fruit varieties were investigated. Quercetin, kaempferol, isorhamnetin, ascorbic acid

and carotenoids were achieved from these extracts. The varieties with red-skin fruits contained the most ascorbic acid (815  $\mu$ g/g fruits weight) and the yellow-skinned fruits (*Opuntia stricta* var. *stricta*) had the most carotenoids (23.7  $\mu$ g/g fw). This study also reported the fact that, the antioxidant capacity of cactus fruits can be related to their flavonoid, ascorbic acid and carotenoid contents. The data exhibited that cactus fruits are a precious source of natural antioxidants [58]. Chang *et al.* evaluated the methanolic extract from betacyanin-free seeds of *OD* for antioxidant activity. The results showed in three assay systems a higher antioxidant capacity for betacyanin-free seeds of *OD* than extracts from peel and pulp with betacyanins. The pulp contains more ascorbic acids than peel and seeds did not contain this valuable vitamin. The extracts obtained from the former have the greater antioxidant capacity than the latter because of a higher amount of total phenolic compounds (133.4 versus 91.5 mg/100 g fresh weight) [43]. Antioxidant activity of this plant in aqueous extractions against lipid peroxidation is also reported [59]. Betanin and isobetanin are two compounds with high amounts of *OD* fruit. It was indicated that these two compounds were considered great free radical scavengers and valuable antioxidant constituted in certain pH levels [60]. It is also suggested that these compounds may be considered as potentially effective bio-molecules for improving human health and preventing disease states [61, 62].

#### 2.4.3. Anti-tumor activity

An investigation showed antitumor effects of polysaccharides isolated from this plant on SK- MES-1 cell lines [63]. Amaresh Mishra has mentioned this plant as an anti-cancer plant [64].

#### 2.4.4. Neuroprotective

Xianju Huang *et al.* evaluated neuroprotective and antioxidant effects of Cactus polysaccharides of *OD* on brain ischemia-reperfusion injury in rats and on the oxidative stress-induced damage in PC12 cells and these compounds isolated from *OD*, were considerable potency for treatment of ischemia and oxidative stress-induced neurodegenerative disease [65]. These results may be due to *OD* valuable compounds such as flavonoids known as great antioxidants [66-69]. Furthermore, these results are correlated with the investigation of polysaccharides isolated from *Opuntia milpa alta* on the H<sub>2</sub>O<sub>2</sub>-induced cortex and hippocampal injury [70]. Other studies on the genus's *Opuntia* have shown neuroprotective effects too [71-73].

#### 2.4.5. Hepatoprotective activity

Published pieces of literature also represented hepatoprotective effects of this plant. Shah *et al.* studied the hepatoprotective effect of fruit pulp extracts of this plant on cadmium-induced toxicity in mice. Their results indicated hepatoprotective of *OD* in hepato-histopathological evaluations [74]. Hepatoprotective effect of polysaccharides obtained from this plant also evaluated by Yu

NingHua *et al.* in the mice model of hepatic injury induced by carbon tetrachloride (CCl<sub>4</sub>). Their results showed that OD polysaccharides could significantly reduce serum ALT and AST activities compared to CCl<sub>4</sub> group and increase the content of liver GSH, GR, GST and GSH-Px activities in liver-injured mice. OD polysaccharides also could ameliorate the hepatic pathological changes [75].

#### 2.4.6. Hypotensive activity

A study conducted by Saleem *et al.* showed that the methanolic extracts of OD cladodes and its pure compounds like  $\alpha$ -pyrone glycoside and opuntioside-I can exert a hypotensive effect in normotensive rats [76]. A review by Talha *et al.* on the herbal hypotensive compounds has reported OD as a plant containing hypotensive properties [77].

#### 2.4.7. In-Vitro antimicrobial synergistic and anti-tubercular (Tb) effects

Investigation of the synergistic antimicrobial and anti-tubercular activities of OD hydro- alcoholic extract conducted by Subal *et al.* showed the inhibitory effect upon this plant [78].

At Another study done by Ratnaweera *et al* Endophytic fungi isolated from the sterilized surface of cladodes and flowers of OD by several nutrient media and their antimicrobial activities were evaluated against two Gram-negative and three Gram-positive bacteria and *Candida albicans*. The results showed that OD harbors several endophytic fungi producing various antimicrobial compounds with selective antibacterial characteristics. It was mentioned that these antimicrobial properties may be due to secondary metabolites produced by these endophytic fungi such as *equisetin* obtained from the endophytic *Fusarium* spp isolated from OD [79].

Javeed *et al* evaluated the Extracts obtained from the dried stem of OD in polar and non-polar based extraction for antimicrobial effects, their results showed that polar extraction of OD exhibits potent antimicrobial effects [80].

#### 2.4.8. Anti-diabetic effect

Perfumi and Tacconi investigated the anti-hyperglycemic effect of OD in normoglycemic and alloxan-induced diabetic rabbits and reported a hypoglycemic effect of this plant. Furthermore, they indicated that this effect is due to reducing intestinal absorption of glucose; however, this may not be the only hyperglycemic action of this plant. For example, this plant may contain some insulin-like compound leading to this effect. This fact should be mentioned that in an oral toxicity study of OD extract, rats given doses of up to 50 ml/kg exhibited no symptoms of toxicity [42, 81]. Ripe fresh fruit of OD in the *Canary Islands* is included in folk medicine as an antidiabetic crude drug [82]. Zhao *et al.* evaluated the efficacy of OD tablet (ODT) in type two diabetes mellitus (DM) patients in a four-week clinical trial. Their results showed that ODT could improve the glycometabolism of DM patients sufficiently and reduce the impairment of renal function in diabetic

neuropathy [83]. Investigation of the possible role of OD fruit juice in the treatment of streptozotocin (STZ)-induced diabetes in rats and additionally nutritive value of the OD fruits by Inas Z. A revealed that oral administration of OD juice to diabetic rats improved lipid profile and body weight gain. It also significantly reduced MDA levels and blood glucose as compared with the non-treated diabetic group [84].

#### 2.4.9. Clinical trials:

Antioxidant activity of extracts obtained from OD Haw fruit (ODHF) and its active compounds on low-density lipoprotein (LDL) peroxidation by Trolox equivalent antioxidant capacity and oxygen-radical absorbance capacity approaches were in the order of seed > peel > pulp. Reduction of lipid peroxidation in human plasma showed that this plant possesses great antioxidant effects [43].

Zhao *et al.* evaluated the effect of OD tablet (ODT) in type two diabetes mellitus (DM) patients in a four-week clinical trial. Their results showed that ODT could improve the glycometabolism of DM patients sufficiently and also reduce the impairment of renal function in diabetic neuropathy [83].

Betanin a compound with the high amount in *Opuntia* species evaluated on myeloperoxidase/nitrite-induced oxidation of human low-density lipoproteins. Their results suggest that betanin scavenges the initiator radical nitrogen dioxide and can also act as a *lipoperoxyl* radical-scavenger obviously state the antioxidant effect of various organs of OD [30, 85].

### 3. Conclusion

OD certainly should be considered as a plant with suitable properties against various diseases (Figure 2). Chiefly nowadays with the great increasing rate of diseases promoted by the lifestyles especially including diabetes and cardiovascular diseases. The adaptation with various environments and great productivity of this plant make it suitable for medicinal researches in order to purify and isolation new pharmacologically valuable compounds with more efficacies in the prevention and treatment of various diseases. In addition to other studies on the genus *Opuntia*, the pharmacologic properties such as anti-hyperlipidemia, anti-atherosclerotic, anti-inflammatory, anti-diabetic, antiviral, antioxidant and anti-ulcerogenic properties were revealed. Vitamins B1, B2, C,  $\beta$  - carotene, E and D3 were observed. The great effectiveness and fewer side effects in comparison to other drugs may be complementary to mention the value of botanic industries and researches revealing the importance of using herbal plants instead of chemical drugs. Unfortunately, this plant is neglected in the sites of origin and found attention at the other regions of the world. At the end we can announce *Opuntia* genus and especially OD as great genus and plant in the *Cactaceae* family needing more investigations to obtain valuable botanic compounds in order to promotion of botanic industries as the future of pharmacopuncture.



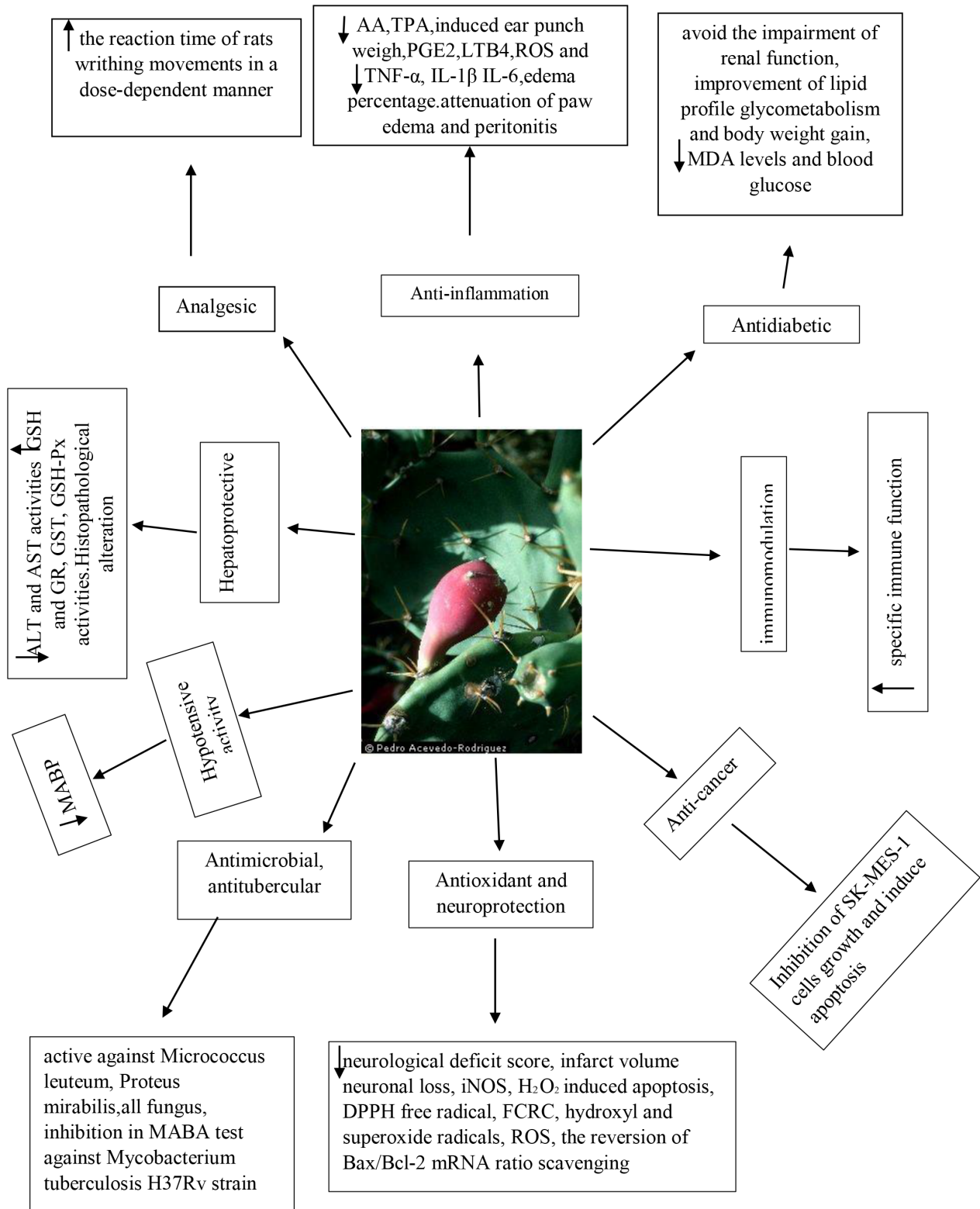


Figure 2 Summarization of OD pharmacologic properties

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