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Review Article

Biological Actions of *Opuntia* Species

Chauhan SP, Sheth NR[1], Jivani NP, Rathod IS[2], Shah PI[3]

Department of Pharmaceutical Chemistry, Smt. R. B. Patel Mahila Pharmacy Collge, Atkot, [1]Department of Pharmaceutical Sciences, Saurashtra University, Rajkot, [2]Department of Pharmaceutical Chemistry, L. M. College of Pharmacy College, Ahmedabad, [3]Department of Pharmacology, S. S. Pharmacy College, Bhavnagar, Gujarat, India

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A B S T R A C T

Plants of *Opuntia* species (Cactaceae) are well-known and important, and are widely used in several indigenous systems of medicine for the treatment of various ailments, viz. asthma, inflammatory diseases, ulcer and diabetes. Different pharmacological experiments in a number of *in vitro* and *in vivo* models have convincingly demonstrated the ability of *Opuntia* species to exhibit various pharmacological activities, lending support to the rationale behind several of its traditional uses. Due to the remarkable biological activity of *Opuntia* and its constituents, it will be appropriate to develop them as a medicine.

Introduction

Phytopharmaceutical products have served as a major source of drugs for centuries and today about half of the pharmaceuticals in use are derived from natural products. The use of phytopharmaceutical substances, particularly isolated from plants, to control diseases is an old practice that has led to the discovery of more than half of all modern pharmaceuticals as complimentary or alternative medicine either to prevent or ameliorate many diseases in recent years.[1] The presence of potentially active nutrients and their multifunctional properties make *Opuntia* spp. fruits and phylloclades perfect candidates for the production of phytopharmaceutical products. Although traditionally appreciated for its pharmacological properties by the Native Americans, cactus pear is still hardly recognized because of insufficient scientific information.[2] However, recent studies on *Opuntia* spp. have demonstrated prickly pear fruit and vegetative cladodes to be excellent candidates for the development of phytopharmaceutical products. Therefore, this review summarizes current knowledge on the biological actions of *Opuntia* spp.

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Correspondence:
Dr. Sanjay P. Chauhan; E-mail: sanjulmcp@rediffmail.com

Opuntia is a large genus of succulent shrubs, native of the new world, now widely grown in the warmer parts of the world on account of their unique appearance and attractive flowers. They are commonly known as prickly pears because of their edible fruits. The cactus *Opuntia* (subfamily: *Opuntioideae*, family: Cactaceae) is a xerophytic plant producing about 200–300 species and mainly grows in arid and semiarid zones. In local parlance, cactus is called prickly pear, slipper thorn, tuna (English) and fico d'india (in Spain), and has different vernacular names in India like Hathlo thor, chorhthlo (Gujarati), Haththathoira, Nagphana, Nagphani (Hindi), Snuhi, Vajrakantaka, Bahushala (Sanskrit), Nagadali, Nagakkali, Chapati balli (Tamil), Nagamulla, Nagajemudu (Telugu), Nagphani, Thuar (Urdu). It was found that cacti in India did not all belong to one species, i.e., *Opuntia dillenii*, but three to four species distributed over different regions in India. *O. dillenii* Haw. was found mainly in the southern parts of the India, while *Opuntia vulgaris* Mill. (Syn *Opuntia monocantha* Haw.) was distributed mainly in the northern parts; *Opuntia elatior* Mill. was found in western India.[3,4]

The plant is bitter and hot, and acts as a laxative, stomachic, carminative, diuretic, antipyretic, alexiteric, and cures biliousness, burning, leukoderma, "vata", urinary complaints, tumors, ascites, loss of consciousness, piles, inflammations, vesicular calculi, anemia, ulcers, bronchitis of children, ophthalmia, liver complaints, lumbago and enlargement of the spleen. The phylloclades (cladodes) are very tasty and stomachic, and cure inflammations, ascites, tumors and pains. The phylloclades, mashed up and applied as a poultice, are said to allay heat and inflammation. The hot leaf applied to boils hastens suppuration; the phylloclade made into a pulp is applied to the eyes in cases of ophthalmia. In South Africa and Australia, a decoction of the phylloclade has been used as a diabetes remedy. A wineglassful of a strong decoction, to which sodium bicarbonate is often added, is taken thrice daily. It must be freshly prepared each day. It is reported from Australia to relieve the symptoms and lower the blood sugar level in diabetes. A second method of preparation is to cover the minced phylloclade with sodium bicarbonate overnight. A black treacly liquid exudes, which is used as a remedy for diabetes. The flowers cure bronchitis and asthma. The fruit is considered as a refrigerant, and is said to be useful in gonorrhea. The baked fruit is given in whooping cough and syrup of the fruit is given to increase the secretion of bile and control spasmodic cough and expectoration. [3-6]

Many species of cactus are found growing either as wild plants in arid and semiarid regions of India or as ornamental plants in urban homes and gardens. Generally, these species are used as live fences to protect agricultural fields from human and animal encroachments with a few exceptions. There has been no attempt to cultivate this plant as a horticultural or fodder crop in India. In countries such as Mexico, USA, Spain, Italy and northern Africa, where the crop is commonly known, it already forms an integral part of the people's dietary requirement. In addition to the excellent quality and flavor of the fresh fruit, the young phylloclades serve both as a vegetable and salad dish and the immature fruit is used to make mock gherkins.[7]

Morphology

Opuntia plants are recognizable cacti growing as small ground-hugging plants to quite massive trees, with the majority growing as erect or trailing shrubs. These perennial plants are typically many branched with distinct jointed, fleshy, flattened, often rounded stem segments, for their photosynthetic function, known as cactus stems, cactus pads, cactus vegetable, phylloclades or cladodes. The stems of prickly pears have varying numbers of areoles, a specialized axillary or lateral bud, short shoot or branch that produce spines and hairs and can produce new stems, flowers or fruits. The subfamily *Opuntioideae* is further characterized by short, sharp, barbed and deciduous spines called glochids. The areoles are irregularly distributed over the stem and are usually elliptic, circular or obovate, and produce white, gray or tan to brown hair and generally two types of spines: large, fixed spines and minute, barbed, hair like spines called glochids that readily detach. The flowers are about 5–6.5 cm long and often showy, radially symmetric and vary in color from yellow, orange, pink to red. The fruits are berry periform, truncate, depressed at the apex, bearing tufts of glochidia on the pericarp, spineless to spiny and range in color from green to yellow, red, orange or purple. Characteristic of *Opuntia* spp. is that many seeds in each fruit have a hard, bony aril or funicular envelope surrounding them.[3,4,8-11]

Biological actions

Opuntia species have been used by humans for thousands of years. Besides being consumed as food or beverages, most portions of the plants have been used as medicine and in modern times have also been prepared as juice, jam, flour, frozen fruit, juice concentrate, and spray-dried juice powder.[2,12-13]

Analgesic and anti-inflammatory

The various fractions of the methanol extract of stems of *Opuntia ficus-india* Mill. were evaluated for their anti-inflammatory action using adjuvant-induced pouch granuloma model in mice and β-sitosterol was identified as an active anti-inflammatory compound.[14] Lyophilized aqueous extract (100–400 mg/kg, i.p.) of the fruits of *O. dillenii* (Ker-Gawl.) Haw. was evaluated for its analgesic activity using writhing and hot plate test in mice and rat, respectively, and also for its anti-inflammatory activity using rats with carrageenan-induced paw edema, and the results showed that it exhibited dose-dependent action.[15]

Anticancer activity

Most recent studies suggest that the cactus pear fruit extract (i) inhibits the proliferation of cervical, ovarian and bladder cancer cell lines *in vitro* and (ii) suppresses tumor growth in the nude mice ovarian cancer model *in vivo*. These experiments showed that inhibition was dose-dependent (1, 5, 10 and 25% cactus pear extract) and time-dependent (1, 3 or 5 day treatment) on *in vitro* cultured cancer cells. The intraperitoneal administration of cactus extract solution to mice did not affect the animal body weight, which indicated that cactus did not have a significant toxic effect in animals. Growth inhibition of cultured-cancer cells was associated with an increase in apoptotic cells and the cell cycle arrest at the G1-phase. Moreover, the induced growth inhibition seems to be dependent on the P53 pathway, which is the major tumor suppressor. Annexin IV increased and the vascular endothelial growth factor (VEGF) decreased in the tumor tissue obtained from animals having received the cactus solution. The antiproliferative effect of betanin, isolated from the fruits of *O. ficus-indica*, was evaluated on human chronic myeloid leukemia cell line (K562). The results show dose- and time-dependent decrease in the proliferation of K562 cells treated with betanin, with an IC_{50} of 40 μM. Further studies involving scanning and transmission electron microscopy (SEM and TEM, respectively) revealed the apoptotic characteristics such as chromatin condensation, cell shrinkage and membrane blebbing. Agarose electrophoresis of genomic DNA of cells treated with betanin showed a fragmentation pattern typical for apoptotic cells. Flow cytometric analysis of cells treated with 40 mM betanin showed 28.4% of cells in sub-G0/G1 phase. Betanin treatment to the cells also induced the release of cytochrome *c* into the cytosol, poly (ADP) ribose polymerase (PARP) cleavage, downregulation of Bcl-2, and reduction in the membrane potentials. These studies demonstrate that betanin induces apoptosis in K562 cells through the intrinsic pathway and is mediated by the release of cytochrome *c* from mitochondria into the cytosol, and PARP cleavage. The mechanisms responsible for executing the antiproliferative effects include: (i) induction of alterations in the cell differentiation pattern, which plays a vital role in the invasiveness and metastatic progression of the tumors, (ii) blockade of pre-neoplastic cell expansion or induction of apoptosis, and (iii) intervention of metabolic activation of carcinogens by scavenging reactive oxygen species (ROS).[16,17]

Antidiabetic activity

The prickly pear cactus stems have been used traditionally to treat diabetes in Mexico.[18] Nowadays, *Opuntia* spp. are amongst the majority of products recommended by Italian herbalists, which may be efficacious in reducing glycemia.[19] Some studies have demonstrated the hypoglycemic activity of the prickly pear cactus extract on non-diabetics and diabetes-induced rats or diabetic humans.[20-24] The anti-hyperglycemic effect of 12 edible plants was studied on rabbits in which were conducted weekly subcutaneous glucose tolerance tests after gastric administration of a juice of stems of *Opuntia streptacantha* (dose 4 ml/kg) which significantly decreased the area under the glucose tolerance curve and the hyperglycemic peak.[25] The hypoglycemic activity of a purified extract from stems of *Opuntia fuliginosa* Griffiths was evaluated on streptozotocin-induced diabetic rats. Blood glucose and glycated hemoglobin levels were reduced to normal values by a combined treatment of insulin and *Opuntia* extract. When insulin was withdrawn from the combined treatment, the prickly pear extract alone maintained normoglycemic state in the diabetic rats. The magnitude of the glucose control by the small amount of *Opuntia* extract required (1 mg/kg b.wt. per day) to control diabetes was in contrast to the high quantities of insulin required for an equivalent effect.[26] Plasma glucose concentrations in streptozotocin-induced diabetic and non-diabetic rats were reduced by the oral administration of *Opuntia megacantha* leaf extracts (20 mg/100 g b.wt.). The results suggest that leaf extracts not only reduce blood glucose levels but also may be toxic to the kidney as shown by the elevation in plasma urea and creatinine concentrations and the reduction of plasma Na^+ concentration.[25] The seed oil from fruits of *O. ficus-indica* is rich in polyunsaturated fatty acids, with an exceptional level of linoleic acid (700 g/kg). In this study, the effect of seed oil supplemented diet on rats was evaluated, and the results indicated a significant decrease in serum glucose concentration (22%) over the control group and an increase in the concentration of glycogen in liver and muscle. Blood cholesterol and low density lipoprotein-cholesterol (LDL-C) decreased in the treated group and high density lipoprotein-cholesterol (HDL-C) concentration increased during the treatment. These findings support the nutritional value of cactus pear as a natural source of edible oil containing essential fatty acids.[27,28]

Anti-hyperlipidemic and anti-hypercholesterolemia activities

Experimental evidence suggests that cactus pear reduces cholesterol levels in human blood and modifies LDL composition.[29-31] The cholesterol, LDL and triglyceride plasma levels of rats were strongly reduced after 30 days of a daily administration (1 g/kg) of lyophilized cladodes of *O. ficus-indica* L. Mill.[32] Sterols which comprise the bulk of the unsaponifiables in many oils are of interest due to their ability to lower blood LDL-C by approximately 10–15% as part of a healthy diet.[33] The effects of diets enriched with cactus pear oil and seeds on serum and liver parameters were studied, and the results indicated a significantly decreased blood cholesterol and LDL-C and increased HDL-C.[27,28,34]

Antioxidant activity

The antioxidative action is one of the many mechanisms by which fruit and vegetable substances might exert their beneficial health effects. The presence of several antioxidants (ascorbic acid, carotenoids, reduced glutathione, cysteine, taurine, and flavonoids such as quercetin, kaempferol and isorhamnetin) has been detected in the fruits and vegetables of different varieties of cactus prickly pear. More recently, the antioxidant properties of the most frequent cactus pear betalains (betanin and indicaxanthin) have been revealed.[35-40] Numerous *in vitro* studies have demonstrated the beneficial effect of phenolics and betalains. These are generally attributed to the ability of antioxidants to neutralize ROS such as singlet oxygen, hydrogen peroxide (H_2O_2), or suppression of the xanthine/xanthineoxidase system, all of which may induce oxidative injury, i.e., lipid peroxidation (LPO). Regular ingestion of prickly pear (*Opuntia robusta*) can significantly reduce *in vivo* oxidation injury in young patients suffering from familial isolated hypercholesterolemia (FH) and oxidation injury determined by 8-epi-$PGF_{2\alpha}$ in plasma, serum and urine. Decrease of 8-epi-$PGF_{2\alpha}$ was more pronounced in females than in males, the highest significance being found in urine, whereas the effects on total cholesterol and LDL-C were more pronounced in males. Thus, this may have a significant cardiovascular benefit.[41] Antioxidant compounds were extracted from the fruit of four *Opuntia* species (*O. ficus-indica, Opuntia lindheimeri, O. streptacantha, Opuntia stricta* var. *stricta*).[42] Zearalenone (ZEN) is one of the most widely distributed fusarial mycotoxins which are encountered in a high incidence in many foodstuffs. In this study, the effect of a single dose of ZEN (40 mg/kg b.wt.) alone and with extract of cactus cladodes (25, 50 and 100 mg/kg b.wt.) on the induction of oxidative stress was monitored in kidney and liver by measuring the malondialdehyde (MDA) level, the protein carbonyls generation, the catalase activity and the expression of the heat shock proteins (Hsp). The results clearly showed that ZEN induced significant alterations in all tested oxidative stress markers, while the combined treatment of ZEN with the lowest tested dose of cactus extracts (25 mg/kg b.wt.) showed a total reduction of ZEN-induced oxidative damage for all tested markers.[43]

The antioxidant and inhibitory effects were investigated using extracts from *O. dillenii* Haw. fruit on LDL peroxidation.[44] The results indicated that the antioxidant activity of methanolic extracts in Trolox equivalent antioxidant capacity and oxygen-radical absorbance capacity assays were in the order of seed > peel > pulp. Among the extracts, seed extracts (10 μg/ml) possessed the highest inhibitory effect on the formation of thiobarbituric acid reactive substances and relative electrophoretic mobility and contained the highest amounts of polyphenols and flavonoids (212.8 and 144.1 mg/100 g fresh seed, respectively).

Antiulcer activity

In Sicily folk medicine, *O. ficus-indica* (L.) Mill. cladodes are used for the treatment of gastric ulcer and its cicatrisant action. The effect of lyophilized cladodes (1 g/kg) on ethanol-induced ulcer in rat was studied and the ultrastructural changes were observed by TEM, confirming the protective effect exercised by administration of lyophilized cladodes. Probably, the mucilage of *O. ficus-indica* was the principal compound for antiulcer action.[45,46]

Antiviral activity

Administration of cactus stem extract (*O. streptacantha*) to mice, horses, and humans inhibits intracellular replication of a number of DNA- and RNA-viruses such as Herpes simplex virus Type 2, Equine herpes virus, pseudorabies virus, influenza virus, respiratory syncitial disease virus and HIV-1.[47] Inactivation of extra-cellular viruses was also reported by the same authors. However, the active inhibitory component(s) of the cactus extract used in this study was not investigated, and as of yet, no further study has dealt with this specific topic. The efficacy of the crude extract of *O. vulgaris* against Newcastle virus disease in domestic fowl in Tanzania was evaluated.[48]

Diuretic activity

The waste matter of cladodes of *O. ficus-indica* (L.) Mill. was studied for its diuretic action in rat. Acute and chronic diuretic activity of 15% infusion of cladodes, flowers and fruits was assayed. Natriuresis, kaliuresis and the activity on fructose-induced hyperuricemia were also studied. The results show that *O. ficus-indica* cladode, fruit and flower infusions significantly increase diuresis. This effect is more marked with the fruit infusion and it is particularly significant during the chronic treatment. The fruit infusion shows also antiuric effect. In this study, cladode, flower and fruit infusions showed a modest but not a significant increase in natriuresis and kaliuresis.[49]

Immunomodulatory effect

Schepetkin provided a molecular basis to explain a portion of the beneficial therapeutic properties of extracts from *Opuntia polyacantha* on human and murine macrophages and demonstrated that all four fractions had potent immunomodulatory activity, inducing production of ROS, nitric oxide, tumor necrosis factor-α (TNFα) and interleukin 6. Modulation of macrophage function by *O. polyacantha* was mediated through activation of nuclear factor κB.[50]

Improved platelet function

Prickly pear is traditionally used by Pima Indians as a dietary nutrient against diabetes mellitus. Wolfram examined the effect of daily consumption of 250 g in eight healthy volunteers and eight patients with mild familial heterozygous hypercholesterolemia on various parameters of platelet function. Beside its action on lipids and lipoproteins, prickly pear consumption significantly reduced the platelet proteins (platelet factor 4 and β-thromboglobulin), ADP-induced platelet aggregation and improved the platelet sensitivity (against PGI_2 and PGE_1) in volunteers as well as in patients. Also, plasma 11-DH-TXB_2 and the WU-test showed a significant improvement in both patients and volunteers. In contrast, collagen-induced platelet aggregation and the number of circulating endothelial cells showed a significant response in the patients only. Prickly pear may induce at least part of its beneficial actions on the cardiovascular system by decreasing the platelet activity and thereby improving the haemostatic balance.[51]

Neuroprotective effect

The flavonoids like quercetin, (+)-dihydroquercetin, and quercetin 3-methyl ether were isolated from ethyl acetate fractions of the fruits and stems of *O. ficus-indica* var. *saboten* and were evaluated for their protective effects against oxidative neuronal injuries induced in primary cultured rat cortical cells and their antioxidant activities were studied using LPO, 1,1-diphenyl-2-picrylhydrazyl (DPPH), and xanthine oxidase (XO) bioassays. Quercetin was found to inhibit H_2O_2- or xanthine (X)/xanthine oxidase (XO)-induced oxidative neuronal cell injury, with an estimated IC_{50} of 4–5 μg/ml and no more protection at concentrations of 30 μg/ml and above, while (+)-dihydroquercetin concentration-dependently inhibited oxidative neuronal injuries, but it was less potent than quercetin. On the other hand, quercetin 3-methyl ether potently and dramatically inhibited H_2O_2- and X/XO-induced neuronal injuries, with IC_{50} values of 0.6 and 0.7 μg/ml, respectively. In addition, quercetin and quercetin 3-methyl ether were shown to inhibit XO activity *in vitro*, with IC_{50} values of 10.67 and 42.01 μg/ml, respectively, and quercetin 3-methyl ether appears to be the most potent neuroprotectant of the three flavonoids isolated from this plant.[52]

The methanol extract of *O. ficus-indica* (MEOF) was examined for its neuroprotective action against neuronal injury induced by *N*-methyl-D-aspartate (NMDA), kainate (KA), and oxygen–glucose deprivation (OGD) in cultured mouse cortical cells and was also evaluated for its protective effect in the hippocampal CA1 region against neuronal damage evoked by global ischemia in gerbils. Treatment of neuronal cultures with MEOF (30, 300, and 1000 μg/ml) inhibited the NMDA (25 μM), KA (30 μM), and OGD (50 minutes) induced neurotoxicity dose-dependently. The butanol fraction of *O. ficus-indica* (300 μg/ml) significantly reduced NMDA (20 μM) induced delayed neurotoxicity by 27%. Gerbils were treated with MEOF every 24 hours for 3 days (0.1, 1.0, and 4.0 g/kg, p.o.) or for 4 weeks (0.1 and 1.0 g/kg, p.o.), and ischemic injury was induced after the last dose. Neuronal cell damage in the hippocampal CA1 region was evaluated quantitatively on the fifth day after the ischemic injury. When gerbils were given doses of 4.0 g/kg (3 days) and 1.0 g/kg (4 weeks), the neuronal damage in the hippocampal region was reduced by 32 and 36%, respectively. These results suggested that the preventive administration of *O. ficus-indica* extracts may be helpful in alleviating the excitotoxic neuronal damage induced by global ischemia.[53]

Antispermatogenic effect

A methanolic extract from *O. dillenii* Haw., defatted with chloroform and petroleum ether, exerted antispermatogenic effects on rats. The flavone derivatives, vitexin and myricetin, were found to be the active principles. When 250 mg extract per kg body weight was applied, the weights of testis, epididymis, seminal vesicle, and ventral prostate were reasonably reduced, that of Sertoli cells, Leydig cells, and gametes also reduced. The motility of the sperms was also diminished.[54]

Wound-healing activity

In traditional medicine, extracts of polysaccharide containing plants are widely employed for the treatment of skin and epithelium wounds and mucous membrane irritation. The extracts of *O. ficus-indica* cladodes are used in folk medicine for their antiulcer and wound-healing activities. The methanolic extract of *Opuntia ficus-indica* stems and its hexane, ethyl acetate, *n*-butanol and aqueous fractions (100 mg/site) exhibited wound-healing activity in rats, which was evaluated by measuring the tensile strength of skin strips from the wound segments. The extract and less polar fractions showed significant effects.[55]

The wound-healing potential of two lyophilized polysaccharide extracts obtained from *O. ficus-indica* (L.) cladodes was studied by applying them on large full-thickness wounds in the rat. The wound-healing effect was more marked for polysaccharides with a molecular weight (MW) ranging 10^4–10^6 Da than for those with MW > 10^6 Da, suggesting that the fine structure of these polysaccharides and their particular hygroscopic, rheologic and viscoelastic properties may be essential for the wound-healing promoter action.[56]

Monoamino-oxidase inhibition

Besides catecholmethyltransferases, the monoamino-oxidases (MAOs) are usually involved in the catabolism of catecholamines, thus regulating the overall amine pool. In cladodes and fruits from the Korean *O. ficus-indica* var. *saboten* Makino, methyl esters derived from organic acids were identified as MAO inhibitors. The aqueous extracts showed least inhibitory activity, followed by the *n*-butanol fraction and the hexane extract, whereas the ethyl acetate fraction exerted the highest inhibitory action. The active agents were identified as 1-methyl malate, 1-monomethyl citrate, 1,3-dimethylcitrate, and 1,2,3-trimethylcitrate. The purified components showed MAO-A inhibitory action with increasing number of methyl substituents, whilst superior MAO-B inhibitory action was shown by 1-methylmalate compared to the mono- and dimethylcitrates. However, 1,2,3-trimethylcitrate exerted the strongest inhibition on both MAOs. When citrate was compared with its corresponding methyl derivatives, the methoxy moiety proved to be the effective moiety.[57]

Nutritional importance

Cacti have long been considered an important nutritional source (bread of the poor) in Latin America, among which *Opuntia* has gained highest economic importance worldwide. It is cultivated in several countries such as Mexico, Argentina, Brazil, Tunisia, Italy, Israel and China. Both fruit and stems have been regarded to be safe for consumption as food. The constantly increasing demand for nutraceuticals is paralleled by a more pronounced request for natural ingredients and health-promoting foods. The multiple functional properties of cactus pear fit well in this trend. Recent data reveal the high content of some chemical constituents, which can give added value to this fruit on a nutritional and technological functionality basis. High levels of betalains, taurine, calcium, magnesium, and antioxidants are noteworthy.[2,12,58]

Conclusion

The *Opuntia* spp. cladodes and fruits serve as a source of varied number of phytoconstituents, mainly sugar, phenolics and pigments. Although the reported evidences provide the effectiveness of *Opuntia* spp., active constituents, bioavailability, pharmacokinetics and physiological pathways for various biological actions are not well known in sufficient detail or with confidence. Still more attention is required toward the development of simple, feasible and cost-effective pharmaceutical preparations of *Opuntia* spp. cladodes and fruit juice, as well as the ethnobotanical approach, if combined with mechanism of action, biochemical and physiological methods, would provide useful pharmacological leads.

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