Pharmacology & Toxicology Research
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Recent Advances in *Opuntia ficus-indica*: Integrating Traditional Knowledge with Contemporary Pharmacological and Toxicological Evidence

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Review Article

How to Cite:
Singh S,Balhara S, Sindhu RK. Recent advances in *Opuntia ficus-indica*: Integrating traditional knowledge with contemporary pharmacological and toxicological evidence. *Pharmacol Toxicol Res.* 2026;2:19-28.

Keywords:
Opuntia ficus-indica, pharmacological profile, phytochemical profile, toxicology

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ABSTRACT

The xerophytic cactus *Opuntia ficus-indica* (L.) Mill., belonging to the family Cactaceae, is widely utilized worldwide for its medicinal, ethnomedicinal and nutritional properties. Various parts of the plant contain a diverse range of bioactive compounds, including fatty acids, vitamins, phenolic acids, betalains (betanin and indicaxanthin), flavonoids (isorhamnetin, quercetin and kaempferol) and phytosterols. A comprehensive literature search was conducted using Scopus, Google Scholar, Web of Science and PubMed to identify relevant published studies. The available evidence demonstrates that *O. ficus-indica* exhibits a broad spectrum of biological activities, including antiulcer, analgesic, antioxidant, immunoprotective, antimicrobial, diuretic, hepatoprotective, nephroprotective, anti-inflammatory, anthelmintic, wound-healing, anti-acetylcholinesterase and antidiabetic effects. These pharmacological activities have been primarily attributed to the plant's high content of polyphenolic compounds and mucilage, which may shows their effects through free-radical scavenging, enhancement of endogenous antioxidant defenses and modulation of inflammatory processes. Toxicological evaluations generally indicate that *O. ficus-indica* is safe for human consumption; however, potential adverse effects and safety concerns should be considered, particularly with excessive or prolonged use.

INTRODUCTION

One of the most widely recognized species of the genus *Opuntia* is *Opuntia ficus-indica* (L.) Mill., a xerophytic cactus belonging to the family Cactaceae and subfamily Opuntioideae. The species is highly water-efficient and exhibits remarkable adaptability to diverse environmental conditions. Although, native to the New World, particularly central Mexico, *O. ficus-indica* has been introduced and extensively cultivated in various regions, including the Mediterranean basin, Africa and Asia. In India, it is locally known by several names, including Nagphani, Hathlo Thor, Chapathi Balli and Nagajemudu. The species possesses several characteristic xerophytic adaptations, including Crassulacean Acid Metabolism (CAM) photosynthesis, a thick cuticle, specialized water-storage tissues and a shallow root system, which enable it to survive and thrive under extremely hot and arid conditions[1,2].

Opuntia ficus-indica is a versatile plant that serves as an important food and feed resource for both humans and animals. Its fruits, commonly known as tunas and young cladodes, referred to as nopalitos, are widely consumed as food. In addition, the plant is utilized as a vegetable, animal feed, natural dye and source of cochineal extract. The seeds are also used in the production of commercial products, including soaps, shampoos and creams, particularly for cosmetic and pharmaceutical applications[3]. In traditional medicine, *O. ficus-indica* has been used for the management of various ailments, including digestive disorders, burns, skin ulcers, asthma and oedema. These traditional applications have been increasingly supported by modern scientific investigations, which have demonstrated a broad range of potential health-promoting effects, including gastroprotective, neuroprotective, anti-inflammatory, antidiabetic and antioxidant activities. Furthermore, extracts of *O. ficus-indica* have demonstrated potential therapeutic applications in the management of several chronic diseases, including diabetes, cancer and cardiovascular disorders[4,5].

The cladodes and fruits of *O. ficus-indica* are characterized by low lipid content and relatively high moisture and carbohydrate contents, supporting their potential as low-calorie food resources[6]. Importantly, the nutritional and functional characteristics of different plant parts are associated with their distinct profiles of bioactive compounds. The cladodes are particularly rich in mucilage, pectin and flavonol glycosides, including isorhamnetin derivatives, whereas the fruits are predominantly characterized by betalains, particularly betanin and indicaxanthin. The fruits also contain appreciable amounts of ascorbate. Despite this chemical diversity, much of the existing literature on the phytochemistry of *O. ficus-indica* has focused either on the whole plant or on individual plant parts without adequately distinguishing their respective chemical compositions and associated biological activities. Moreover, important factors that can influence phytochemical composition and biological activity, including genotype, developmental stage and the solvent used for extract preparation, have frequently received insufficient consideration. Therefore, a comprehensive comparative synthesis is needed to integrate the fragmented evidence and elucidate the molecular mechanisms underlying the reported biological activities of *O. ficus-indica*[7-10].

The biological and morphological characteristics of *O. ficus-indica* are summarized in Table 1.

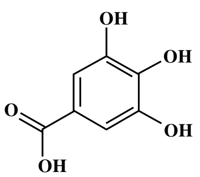
Phytochemical profile: *Opuntia ficus-indica* is a highly adapted xerophytic species that exhibits remarkable tolerance to water scarcity and other adverse environmental conditions. Its adaptation to arid and stressful environments has contributed to the development of a diverse and complex phytochemical profile, comprising a wide range of primary and secondary metabolites[1,2]. The distribution of these bioactive constituents is not uniform across the different plant organs. In particular, cladodes, fruits and flowers contain distinct profiles of secondary metabolites, including polyphenols, betalains and vitamins, which accumulate in a tissue-specific manner[7,11].

The cladodes are characterized by high concentrations of mucilage, pectin and isorhamnetin glycosides, whereas the fruits are particularly rich in the betalains betanin and indicaxanthin[7,8]. The seeds constitute an important source of essential fatty acids and phytosterols[12,13]. This complex and organ-specific phytochemical composition, which is further influenced by factors such as genotype and developmental or maturity stage, provides a potential mechanistic basis for the broad spectrum of pharmacological activities attributed to *O. ficus-indica*[7,14]. The major phytoconstituents identified in *O. ficus-indica* are summarized in Table 2.

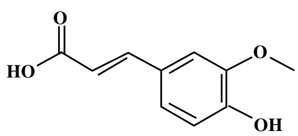
Table 1: Botanical identity and key morphological features of *Opuntia ficus- indica*

Aspect	Description	References
Taxonomy	Family Cactaceae; subfamily Opuntioideae; genus *Opuntia*; species *Opuntia ficus- indica* (L.) Mill	1
Morphology	Succulent, flattened cladodes perform photosynthesis and water storage; flowers and berries arise from areoles on cladode margins	1
Common names	Prickly pear, Indian fig, Cactus pear, Nagphani, Nopal and regional variants	1
Main tissues	Cladodes, fruit seeds, fruit peel, pulp and flowers	3

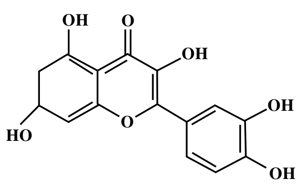
Important structures of some major phytoconstituents:



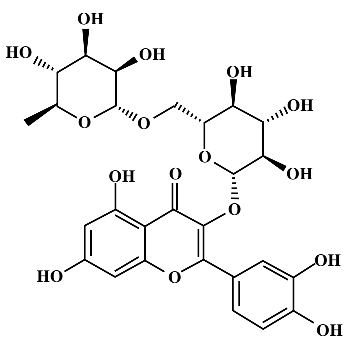
Gallic acid



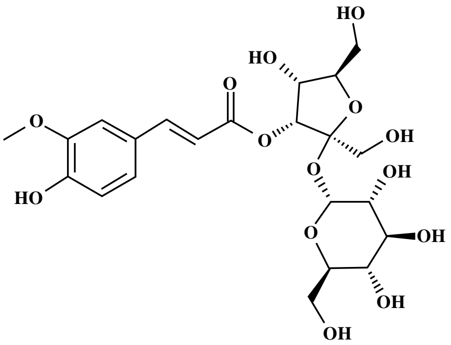
Ferulic acid



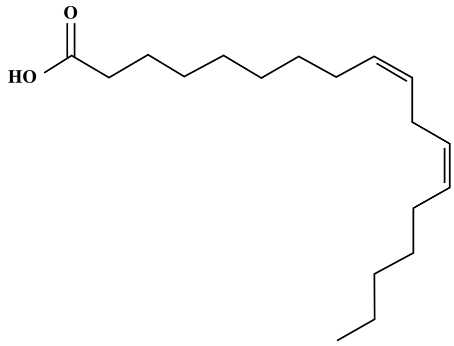
Quercetin



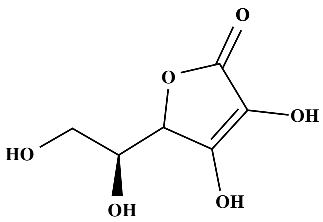
Rutin



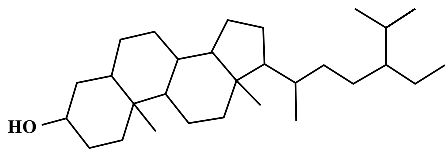
Feruloyl-sucrose isomer 1



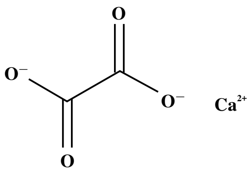
Linoleic acid



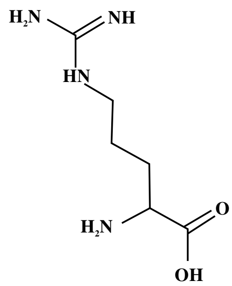
Vitamin C (ascorbic acid)



Beta-sitosterol



Calcium oxalate



Arginine

Table 2: Major phytoconstituents of *opuntia ficus-indica*

Phytochemical class	Major phytoconstituents	Plant part(s)	References
Phenolic Acids	Gallic acid,4-Hydroxybenzoic acid, 3,4-Dihydroxybenzoic acid Ferulic acid, Salicylic acid, Coumaric acid	Flowers, Cladodes	44-50
Flavonoids	Quercetin, Quercetin 3-O-rutinoside, Quercetin 3-O-glucoside, Isorhamnetin, Isorhamnetin 3-O-galactoside, Isorhamnetin 3-O-robinobioside, Isorhamnetin 3-O-glucoside, Kaempferol, Kaempferol 3-O-arabinoside, Isoquercetin, Nicotiflorin, Rutin, Narcissin, Kaempferol 3-O-rutinoside,	Flowers, Pulp, Fruit Peel, Cladodes	44,45,47,48,50-58
Phenolic Derivatives	Feruloyl-sucrose isomer 1, Sinapoyl-diglucoside, Feruloyl-sucrose isomer 2,	Seeds	13
Fatty Acids	Palmitic acid, Palmitoleic acid, Myristic acid, Stearic acid, Oleic acid, Linoleic acid, Arachidic acid, Linolenic acid, Behenic acid, Erucic acid, Lauric acid, Lignoceric acid	Cladodes, Seeds, Fruit Pulp, Fruit Peel	12, 59-61
Vitamins	α-Tocopherol, β-Tocopherol, γ-Tocopherol, δ-Tocopherol, Vitamin B, Vitamin B1, Vitamin K1, Vitamin B2, Vitamin B3	Fruit peel, Seeds, Fruit Pulp, Cladodes	62,63
Phytosterols	Campesterol, Lanosterol, β-Sitosterol, Stigmasterol, Ergosterol, Δ5-Avenasterol, Δ7-Avenasterol	Fruit Pulp, Seeds, Fruit Peel	12,64
Minerals	Magnesium, Sodium, Potassium, Iron, calcium, Phosphorus, Zinc, Manganese, Calcium oxalate, manganese	Fruit Pulp, Seeds, Cladodes	42,62,65-68
Amino Acids	Alanine, Asparagine, Aspartic acid, Arginine, Glutamine, Glutamic acid, Cystine, Histidine, Leucine, Lysine, Methionine, serine, Isoleucine Phenylalanine, Threonine, Tyrosine, Tryptophan, α-Aminobutyric acid, Carnosine, Citrulline, Ornithine, Proline, Taurine, Glycine, Valine	Cladodes, Fruit Juice, Seeds	62,63

Traditional uses: *Opuntia ficus-indica* (L.) Mill. is a species of considerable ethnobotanical importance and has a long history of use in traditional Mexican, Latin American, African and Mediterranean medicine[15,16]. Various parts of the plant have traditionally been employed for the management of a broad range of health conditions. The cladodes, commonly known as nopales, are applied topically to burns, wounds and skin irritations, whereas their oral use has been reported for the management of oedema, gastric ulcers and indigestion. Broiled cladodes and fruits have also traditionally been used to manage diabetes and hyperlipidemia, as well as bronchial asthma, gonorrhea and diarrhea. The flowers are used in the preparation of diuretic herbal teas, including preparations traditionally administered to teething infants. In addition, *O. ficus-indica* has been traditionally used for the management of whooping cough, rheumatism, hypertension and glaucoma[3]. The longstanding use of this plant in traditional medicine has been associated with its perceived safety, therapeutic efficacy and broad medicinal potential[17,18]. However, traditional applications should be interpreted in conjunction with pharmacological and toxicological evidence to establish their therapeutic relevance and safety.

Pharmacological activities: *Opuntia ficus-indica* (L.) Mill. is regarded as a multifunctional botanical resource with a broad spectrum of biological and pharmacological activities demonstrated in various *in vitro* and *in vivo* experimental models. The following sections provide a comprehensive overview of the reported pharmacological effects of *O. ficus-indica*, with emphasis on the underlying mechanisms, bioactive constituents and plant tissues associated with these activities.

Anti-ulcer activity: The fruits and cladodes of *O. ficus-indica* have demonstrated gastroprotective and anti-ulcer activities through several mechanisms. In rat models of pylorus ligation- and ethanol-induced gastric ulceration, oral administration of aqueous or ethanolic fruit extracts at a dose of 250 mg/kg produced significant gastroprotective effects. Compared with the negative control group, treatment with the ethanolic extract reduced the ulcer index by 55.6%. The observed gastroprotective activity was associated with reduced gastric acidity, increased gastric pH and enhanced mucus production, as indicated by an increase in total carbohydrate content accompanied by a reduction in total protein content. Polyphenols, flavonoids and terpenoids may contribute to these effects through their antioxidant and free-radical-scavenging properties[19].

Cladode-derived mucilage and dehydrated cladode powder have also demonstrated anti-ulcer effects. Administration at 1 g/kg significantly reduced the ulcer index from 8.6 in the negative control group to 1.7 in the mucilage-treated group and 2.1 in the dehydrated powder-treated group. The gastroprotective mechanism may involve the formation of a physical barrier by the highly viscous and polymeric mucilage, thereby protecting the gastric mucosa from damaging agents. In addition, the antioxidant properties of cladode constituents may contribute to restoration of superoxide dismutase activity. At a dose of 1 g/kg, the preventive effects were more pronounced than the curative effects. Collectively, these findings suggest that *O. ficus-indica* may have potential as a complementary or alternative therapeutic resource for the management of peptic ulcers[20].

Analgesic activity: Ammam et al.[10] investigated the analgesic activity of *O. ficus-indica* using a methanolic extract prepared from shade-dried and powdered cladodes. Administration of the extract at 40 mg/kg significantly reduced pain responses in both Wistar rats and Swiss mice, as demonstrated by the formalin and acetic acid-induced writhing tests. The extract also exhibited analgesic activity in the hot-plate test by significantly increasing the latency to the pain response. Its analgesic effect was reported to be comparable to that of the reference analgesic agents aspirin and pentazocine. These findings indicate that *O. ficus-indica* cladode extract possesses promising analgesic activity and may warrant further investigation as a potential source of analgesic bioactive compounds[10].

Antioxidant activity: The antioxidant activity of *O. ficus-indica* appears to be particularly pronounced in young cladodes and fruit peels. *In vitro* studies employing the DPPH, ABTS and FRAP assays have demonstrated substantial antioxidant capacity, with a total phenolic content of 18.9 g GAE/kg dry weight reported for these tissues[11]. The antioxidant effects are attributed to several complementary mechanisms, including direct scavenging of reactive oxygen species, metal-ion chelation and stimulation of endogenous antioxidant defense enzymes[21].

Clinical investigations have also provided evidence of systemic antioxidant effects following consumption of *O. ficus-indica*. Intake of 300 g of the plant was reported to increase plasma antioxidant activity substantially within three days. These antioxidant effects may contribute to protection of the liver, kidneys and immune system against oxidative damage induced by toxic agents such as ethanol and cisplatin, primarily by reducing lipid peroxidation. However, the antioxidant effects of *O. ficus-indica* may exhibit a hormetic or biphasic dose-response relationship. While doses of 100–200 mg/kg have been reported to exert protective effects, higher doses, such as 400 mg/kg, may produce paradoxical pro-oxidant effects, potentially as a consequence of redox cycling involving phenolic compounds[8]. Overall, the antioxidant properties of *O. ficus-*

ndica have been associated with protection against oxidative damage induced by ethanol, cisplatin and aflatoxin B1, as well as with attenuation of lipid peroxidation in the liver, kidneys and immune system[22,23].

Immunoprotective activity: The immunoprotective activity of *Opuntia ficus-indica* (L.) Mill. has been investigated using aqueous extracts prepared from young cladodes (2-3 weeks old). Male Wistar rats pretreated with chlorpyrifos were administered the extract orally at a dose of 100 mg/kg for 30 days. Treatment attenuated chlorpyrifos-induced immunotoxicity, as evidenced by increased numbers of bone marrow cells and thymocytes and restoration of the microarchitecture of the spleen and thymus. The extract also reduced DNA fragmentation and oxidative damage by modulating the activities of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and by reducing lipid peroxidation. These immunomodulatory and antioxidant effects have been attributed, at least in part, to the phenolic acids and flavonoids present in the extract[24].

Antimicrobial activity: The antimicrobial activity of *O. ficus-indica* varies according to the microbial strain, plant tissue, maturity stage and extraction conditions. Available evidence suggests that extracts prepared from fruit peels and immature cladodes generally exhibit comparatively strong antimicrobial activity[25]. Ethanolic extracts have demonstrated inhibitory zones of 21.9 mm against *Bacillus subtilis* and 23.52 mm against *Streptococcus pneumoniae*, as determined using broth microdilution and agar well diffusion assays. In some experimental conditions, these effects were reported to be greater than those observed with the reference antibiotics vancomycin and tetracycline. Antimicrobial activity also appears to be influenced by tissue maturity. For example, mature tissues exhibited a Minimum Inhibitory Concentration (MIC) of 1500 µg/mL, whereas extracts of immature cladodes inhibited the growth of *Staphylococcus aureus* at an MIC of 1000 µg/mL[26].

The antimicrobial potential of *O. ficus-indica* may also involve inhibition of microbial adhesion to host tissues, which could contribute to its antiseptic properties. In addition, the essential oil obtained from the seeds demonstrated pronounced antiyeast activity against *Saccharomyces cerevisiae*, producing inhibition zones of approximately 38–40 mm. The antimicrobial effects of *O. ficus-indica* have been associated with its diverse polyphenolic constituents, including isorhamnetin derivatives, other flavonoids and tannins. These compounds may interfere with microbial growth through interactions with nucleic acids, disruption of cellular processes and modulation of extracellular enzyme activity[25].

Antibacterial activity: The antibacterial activity of *O. ficus-indica* (L.) Mill. has been evaluated using various *in vitro* experimental models. Fruit peel extracts have demonstrated antibacterial activity against several clinically relevant bacterial species, including *Salmonella Typhi*, *Bacillus subtilis*, *Streptococcus pneumoniae* and *Escherichia coli*. The agar well diffusion method has commonly been employed to assess this activity using extracts prepared with ethanol, methanol and chloroform. The magnitude of the antibacterial effect varies according to the bacterial species and extraction solvent, ranging from mild to pronounced activity.

Among the tested preparations, the ethanolic extract produced maximum inhibition zones of 23.52 mm against *S. pneumoniae* and 21.90 mm against *B. subtilis*. Notably, the fruit peel extract demonstrated greater inhibitory activity against *S. Typhi*, *B. subtilis* and *S. pneumoniae* than the reference antibiotics tetracycline and vancomycin under the experimental conditions. The reported minimum inhibitory concentrations ranged from 2.75% to 14.13%, with Gram-positive bacteria generally exhibiting greater susceptibility. The antibacterial activity of *O. ficus-indica* is considered to be associated with its diverse array of secondary metabolites[26].

Diuretic activity: The diuretic activity of agro-industrial by-products of *O. ficus-indica* (L.) Mill. has been evaluated in male Wistar rats weighing 150-200 g under standardized experimental conditions. Both acute administration [single oral dose of 5 mL/100 g] and chronic administration [1.5 mL/100 g daily for seven consecutive days] were investigated. Three preparations were evaluated according to procedures described in the Italian Pharmacopoeia: A centrifuged suspension of fruit pulp, air-dried flowers and a 15% aqueous infusion prepared from cladodes after removal of the epidermis and glochids. Hydrochlorothiazide administered at 10 mg/kg was used as the reference diuretic.

Diuretic activity was assessed by measuring 24-h urine volume and urinary sodium and potassium excretion. In addition, an experimental model of fructose-induced hyperuricemia was used to evaluate potential antiuric effects. Among the preparations tested, the fruit infusion exhibited the greatest diuretic activity, increasing the 24-h urine volume by 42.9% compared with the control value, corresponding to 24.2±0.6 mL. It also modified sodium and potassium excretion in the experimental animals in a manner comparable to the reference treatment ($p<0.05$)[27]. Furthermore, the fruit infusion demonstrated a specific antiuric effect, characterized by increased urinary uric acid excretion and reduced plasma uric acid concentrations compared with the control group[28,29].

Hepatoprotective and nephroprotective activities: *Opuntia ficus-indica* (L.) Mill. has demonstrated hepatoprotective and nephroprotective effects in *in vivo* experimental models, indicating its potential to preserve organ integrity against chemically induced injury, including damage caused by nickel sulfate (NiSO) and acetaminophen (APAP). In female Wistar rats, daily administration of mature cladode juice at 10 mL/kg for 30 days substantially attenuated NiSO -induced hepatic injury. Histopathological examination demonstrated improvement in severe hepatic lesions, including portal inflammation and interface hepatitis, while biochemical analyses showed modulation of plasma biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Chromatographic analyses identified ellagic acid, piscidic acid, isorhamnetin-3-O-neohesperoside and *p*-coumaric acid as major bioactive constituents of the juice. Molecular docking studies further suggested strong binding affinities of ellagic acid and *p*-coumaric acid toward alanine transaminase[30].

In a separate experimental model, pretreatment with aqueous *O. ficus-indica* fruit extracts at 100 and 200 mg/kg for seven consecutive days substantially attenuated APAP-induced structural and functional renal impairment in male Sprague-Dawley rats. The elevated serum creatinine (CREA) and blood urea nitrogen (BUN) concentrations induced by APAP intoxication were restored toward normal values following *O. ficus-indica* pretreatment. The nephroprotective effect was associated with reduced lipid peroxidation, as indicated by decreased malondialdehyde (MDA) levels, together with enhanced activities of endogenous antioxidant enzymes, particularly SOD and CAT. These findings suggest that the protective effects of *O. ficus-indica* are mediated, at least in part, through modulation of the endogenous antioxidant defense system.

Notably, the protective activity exhibited a dose-dependent and biphasic, or hormetic, response. Although doses of 100 and 200 mg/kg exerted protective effects, pretreatment with the highest dose tested (400 mg/kg) failed to provide protection and instead produced a pro-oxidant response[31]. This paradoxical effect may be attributable to redox cycling of phenolic antioxidants at high concentrations[14]. Collectively, these findings indicate that *O. ficus-indica* fruit and cladode preparations possess promising hepatoprotective and nephroprotective potential, particularly through their capacity to modulate endogenous antioxidant defenses and mitigate oxidative stress[31].

Anti-inflammatory activity: Indicaxanthin (Ind), a betalain pigment naturally present in cactus pear fruits, has demonstrated significant anti-inflammatory activity in an *in vitro* model of intestinal inflammation using Caco-2 cells stimulated with 25 ng/mL interleukin-1β (IL-1β). IL-1β stimulation increased the secretion of the pro-inflammatory cytokines IL-6 and IL-8 by approximately 10-fold and 24.8-fold, respectively. Treatment with Ind at nutritionally relevant concentrations ranging from 5-25 μM significantly attenuated these responses. At 25 μM, Ind reduced IL-6 and IL-8 secretion by approximately 75% and 65%, respectively. Ind also attenuated the IL-1β-induced increases in nitric oxide (NO) and prostaglandin E2 (PGE2), which increased by approximately 2-fold and 5.2-fold, respectively. Treatment with 10 μM Ind completely inhibited NO production, whereas 25 μM Ind reduced PGE2 production by approximately 70%. Furthermore, 25 μM Ind preserved epithelial barrier integrity by preventing the approximately 30% reduction in transepithelial electrical resistance (TEER) induced by IL-1β stimulation. These anti-inflammatory effects were associated with suppression of the nuclear factor kappa B (NF-κB) signaling pathway and inhibition of NADPH oxidase 1 (NOX1) activation, resulting in reduced expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)[32].

Anthelmintic activity: *Opuntia ficus-indica* has demonstrated noticiable anthelmintic activity against gastrointestinal nematodes of sheep, particularly *Haemonchus contortus*, suggesting its potential as a natural alternative or complementary resource to conventional anthelmintic agents. Among the fractions obtained from 70% ethanolic extracts of cladodes and fruits, the residual aqueous fractions exhibited the greatest activity. The fruit-derived aqueous fraction demonstrated greater ovicidal efficacy, with an EC of 1.5 mg/mL, compared with 7.12 mg/mL for the corresponding cladode fraction. Furthermore, fruit fractions obtained using hexane, water and ethyl acetate, as well as the aqueous cladode fraction, achieved complete (100%) inhibition of larval development at concentrations as low as 1.56 mg/mL. The fruit extract also exhibited greater inhibitory activity against larval migration, with an EC of 0.27 mg/mL, compared with 0.74 mg/mL for the cladode extract.

The anthelmintic activity may be associated with several phytochemicals, including saponins and tannins. Saponins may disrupt parasite cell membranes, thereby facilitating the penetration of tannins and their interaction with intracellular proteins. Importantly, *O. ficus-indica* is also used as a non-toxic forage resource and can constitute up to 56% of the diet of sheep without producing apparent adverse effects. Therefore, its dual potential as a nutritional resource and a natural aid in parasite control warrants further investigation[33].

Wound-healing activity: *Opuntia ficus-indica* has a long history of traditional use for the treatment of burns and various skin disorders. Experimental evidence supports these traditional applications by demonstrating its ability to enhance several physiological processes involved in tissue repair. Methanolic stem extracts containing bioactive constituents such as α-amyrin and β-sitosterol have been reported to significantly increase the tensile strength of healing tissue, an important indicator of collagen maturation and tissue remodeling[34].

Polysaccharide-rich cladode extracts, including TPL-Ofi, may influence both the proliferative and inflammatory phases of wound healing. These extracts have been reported to reduce oedema and hyper nociception while enhancing endogenous antioxidant defenses through increased glutathione (GSH) levels. In addition, they promote tissue regeneration by increasing the number of fibroblasts and myofibroblasts, stimulating neoangiogenesis and upregulating fibroblast growth factor 2 (FGF-2), a key mediator of vascular regeneration and cellular proliferation. The mucilaginous polysaccharides present in *O. ficus-indica* may provide an additional physical advantage by forming a protective molecular network that retains moisture within the wound bed, thereby supporting a favorable environment for tissue repair. Prolonged topical administration of these extracts was reported to be well tolerated, with no adverse effects on systemic homeostasis, body weight, organ mass, or biochemical parameters[35].

Anti-acetylcholinesterase activity: *Opuntia ficus-indica* represents a promising natural source of bioactive compounds for neuroprotective research, particularly in the context of Alzheimer's disease, owing to its inhibitory activity against acetylcholinesterase (AChE). This activity appears to be particularly pronounced in extracts prepared from the flowers and fruit peels. Using the Ellman colorimetric assay, *in vitro* evaluation of aqueous flower and fruit-peel infusions demonstrated that the flower extract exhibited approximately twice the inhibitory potency of the fruit-peel extract, with IC values of 0.26 and 0.49 g/L, respectively.

The observed AChE inhibitory activity was strongly associated with the presence of specific flavonoids and phenolic acids, including myricetin, which was particularly abundant in the flowers and chlorogenic acid, which was prominent in the fruit peels, together with various quercetin and isorhamnetin glycosides. Notably, the flower infusion retained substantial anti-AChE activity during simulated gastrointestinal digestion, with approximately 79.9% of the initial activity remaining after four hours of gastric digestion. These findings suggest that *O. ficus-indica* extracts contain potentially bioavailable phytochemicals capable of inhibiting AChE and may therefore warrant further investigation as natural sources of compounds with potential neuroprotective applications[36].

Antidiabetic activity: Aqueous extracts of fresh nopal cladodes (NPWE) have demonstrated significant α-glucosidase inhibitory activity *in vitro*, with an IC value of 67.33 μg/mL. This inhibitory effect may delay the intestinal hydrolysis of complex carbohydrates into absorbable monosaccharides and thereby contribute to the modulation of postprandial glucose levels[37]. In *in vivo* studies using alloxan-induced diabetic Wistar rats, oral administration of *O. ficus-indica* fruit juice or cladode preparations at 5 mg/kg for four weeks significantly reduced fasting blood glucose (FBG) concentrations, with fruit juice producing a maximum reduction of 59.6%. Furthermore, administration of NPWE at 100 mg/kg significantly improved glucose tolerance and reduced blood glucose concentrations by approximately 19% at key measurement points in Sprague-Dawley rats with a type 2 diabetes-like phenotype induced by a high-fat diet and low-dose streptozotocin (STZ)[38].

In addition to improving glycemic control, *O. ficus-indica* preparations have demonstrated beneficial effects on metabolic and organ-function parameters associated with diabetes. Treatment significantly improved lipid profiles, particularly by reducing total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations. It also normalized hepatic enzyme activities, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and improved renal function, as evidenced by a 38.16% reduction in serum urea concentrations[39]. These findings suggest that *O. ficus-indica* may exert both glucose-lowering and protective metabolic effects in experimental models of diabetes.

The antidiabetic effects of *O. ficus-indica* are likely associated with its high soluble dietary fiber content, reported to account for approximately 45.92% of NPWE, together with its abundance of polyphenols and flavonoids, particularly isorhamnetin and quercetin[37]. These constituents may contribute to improved insulin sensitivity, modulation of carbohydrate digestion and protection of pancreatic β-cells against oxidative stress, thereby providing a potential mechanistic basis for the observed antidiabetic effects.

Toxicological and safety profile: *Opuntia ficus-indica* (L.) Mill. has a long history of use as a food source and the available evidence generally supports its favorable safety and toxicological profile[5]. This apparent tolerability is supported by experimental studies in mice, in which daily oral administration of cladode juice at 10 mL/kg for 30 days produced no mortality or detectable adverse effects on body weight or metabolic parameters[2]. In addition to its general tolerability, *O. ficus-indica* has demonstrated protective effects against several chemically induced toxicities, including immunotoxic and hepatotoxic effects associated with exposure to chlorpyrifos, zearalenone and nickel sulfate[24,30,40,41].

Nevertheless, potential safety considerations should be taken into account, particularly when concentrated extracts or high doses are consumed. Cladodes contain appreciable amounts of calcium and calcium oxalate, which may warrant caution with excessive intake or highly concentrated preparations[42]. The relatively high sugar content of the fruits may also be a concern when consumed in excessive quantities, particularly in individuals requiring strict dietary control of sugar intake[16].

Importantly, experimental studies indicate that *O. ficus-indica* extracts may exhibit a hormetic or biphasic dose-response relationship. Administration of 100-200 mg/kg produced protective effects in experimental animals, whereas a higher dose of 400 mg/kg failed to provide protection and instead induced an oxidative stress response. This paradoxical effect has been attributed to the high concentration of phenolic compounds at elevated doses, which may undergo redox cycling and exert pro-oxidant effects[31].

Although the cladodes and fruits of *O. ficus-indica* are generally considered safe for consumption, a rare but serious case of colonic obstruction has been reported following the ingestion of large quantities of seeds[43]. Consequently, appropriate quality control and pharmaceutical standardization of *O. ficus-indica* extracts are essential, particularly for preparations intended for therapeutic use. Such standardization should include assessment and control of potentially toxic constituents, heavy metals, microbial contaminants, pesticides and other undesirable impurities to ensure consistent quality and safety[23].

CONCLUSION

Opuntia ficus-indica is one of the most adaptable and widely utilized cactus species, with a well-established ethnobotanical history that is increasingly supported by contemporary pharmacological research. Its diverse phytochemical composition, including polyphenols, flavonoids, betalains, vitamins and other bioactive constituents, has been associated with a broad spectrum of biological activities, particularly anti-inflammatory, antidiabetic, antioxidant, gastroprotective, neuroprotective and wound-healing effects. Importantly, the distribution of bioactive compounds varies among plant organs, with cladodes, fruits, flowers and seeds exhibiting distinct phytochemical profiles and biological properties.

Although, individual plant tissues possess specific health-promoting properties, the available evidence also highlights substantial variability related to genotype, maturity stage, extraction procedures and dose. The identification of hormetic or biphasic dose-response relationships further emphasizes the need for careful dose optimization and rigorous standardization when *O. ficus-indica* is developed as a medicinal or nutraceutical resource. Comprehensive quality control is therefore essential to ensure the consistency, efficacy and safety of *O. ficus-indica*-derived products.

Future comparative studies integrating phytochemical profiling, molecular mechanisms, pharmacological evaluation and toxicological assessment across different plant organs will be important for clarifying the relationships between specific bioactive constituents and their biological effects. Such investigations may facilitate the development of standardized *O. ficus-indica*-based phytopharmaceuticals and nutraceuticals with evidence-based applications in the prevention and management of complex chronic diseases and other major global health challenges.

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