

From Traditional Use to Molecular Mechanisms: A Critical Review of the Pharmacological Potential of *Opuntia cochenillifera* (L.) Mill.

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Abstract

The escalating global burden of antimicrobial resistance, chronic inflammatory disease and metabolic disorders has intensified the search for structurally diverse bioactive compounds from medicinal plants. *Opuntia cochenillifera* (L.) Mill. (syn. *Nopalea cochenillifera*), a succulent cactus native to Mexico and widely naturalized across tropical and subtropical regions, is a historically important yet pharmacologically underexplored member of the Cactaceae. This review consolidates and critically evaluates the species-specific botanical, ethnobotanical, phytochemical, pharmacological and toxicological evidence published between 2015 and 2026. The cladodes contain a distinctive phytochemical profile dominated by phenolic acids, including gallic acid (2708.49 microg/g), ferulic acid (796.73 microg/g), chlorogenic acid (179.70 microg/g), p-coumaric acid (80.58 microg/g), syringic acid (11.12 microg/g) and neochlorogenic acid (9.52 microg/g), together with isorhamnetin-3-O-(2",3"-O-di-rhamnose)-glucoside as the major polyphenolic peak, and a polysaccharide-rich mucilage with a water-holding capacity of 2.78 g/g and an oil-holding capacity of 1.80 g/g. The most robust evidence supports anti-inflammatory and gastroprotective activities mediated through downregulation of NF- κ B p65 and MAPK1/ERK2 signalling, reduction of IL-1 β and TNF- α , elevation of IL-10, and attenuation of MDA and MPO. Antimicrobial and antioxidant findings remain inconsistent and are strongly influenced by extraction solvent, plant part and assay methodology. Emerging evidence supports antihyperglycaemic effects that appear independent of potent α -glucosidase inhibition, together with mucilage biocompatibility suited to biomedical applications and accelerated wound healing in diabetic models. An acute toxicity study at 2000 mg/kg revealed no mortality or adverse biochemical or haematological alterations. Nevertheless, methodological heterogeneity, limited bioassay-guided fractionation, the absence of clinical trials and persistent taxonomic confusion between *O. cochenillifera* and its synonym *N. cochenillifera* constrain direct comparison and translational extrapolation. Future investigations should prioritize taxonomically authenticated material, chemically standardized extracts, network-pharmacology-guided mechanistic studies, and rigorous preclinical dose-response and toxicological evaluation as prerequisites for clinical translation.

Keywords: *Opuntia cochenillifera*; *Nopalea cochenillifera*; Ethnopharmacology; Phenolic Compounds; Anti-Inflammatory Activity; NF- κ B; MAPK Signalling; Mucilage; Polypharmacology; Network Pharmacology

1. Introduction

Medicinal plants continue to serve as an indispensable reservoir of structurally diverse natural products for modern pharmacotherapy. Natural products and their derivatives account for a substantial proportion of all small-molecule drugs approved over the past four decades, and they remain a dominant source of first-in-class therapeutic agents (Atanasov et al., 2021; Newman and Cragg, 2020) [1, 2]. The World Health Organization (WHO) estimates that a large majority of the global population relies on traditional medicine for at least part of its primary healthcare, while simultaneously declaring antimicrobial resistance one of the top global public health threats facing humanity (WHO, 2024) [3]. In parallel, the rising prevalence of chronic non-communicable diseases, including inflammatory bowel disease, type 2 diabetes mellitus and gastric mucosal disorders, has intensified the search for novel bioactive compounds from historically documented botanical sources.

Succulent species of the family Cactaceae have attracted renewed scientific attention because they integrate remarkable physiological adaptations with nutritional, ethnobotanical and potential pharmaceutical value. The genus *Opuntia* is particularly significant, given its long history of use as food, fodder, ornamental plant and traditional medicine across the Americas, Africa, Asia and the Mediterranean basin (Del Socorro Santos Diaz et al., 2017) [4]. A critical caveat pervades this literature: pharmacological findings obtained in one *Opuntia* species cannot be extrapolated to another without rigorous experimental verification, because congeners differ substantially in phytochemical composition, activity profiles and responses to extraction and experimental conditions (Heinrich et al., 2022) [5]. *Opuntia cochenillifera* (L.) Mill. whose nomenclatural synonym *Nopalea cochenillifera* (L.) Salm-Dyck is still widely used in the pharmacological literature (Royal Botanic Gardens, Kew, 2026) [10], exemplifies this challenge.

Native to Mexico and historically introduced throughout tropical Asia, Africa, the Caribbean and the Pacific, *O. cochenillifera* possesses multiple documented traditional uses, including food, animal feed, medicine and its role as a host for cochineal insects in natural dye production [10]. In the Philippines it is known as dilang-baka and has been used in traditional water purification, whereas in Brazil, where it is called palma or palma doce, the cladodes are consumed as food and used in traditional medicine for inflammatory conditions, diabetes and gastrointestinal complaints (Guerra et al., 2022; Tavares et al., 2023a) [13, 21]. Despite this ethnobotanical significance, *O. cochenillifera* remains pharmacologically underexplored relative to more intensively studied congeners such as *O. ficus-indica*. The existing literature is fragmented and is characterized by contradictory antimicrobial and antioxidant findings, limited species-specific phytochemical characterization and a near-total absence of clinical investigation. Contemporary natural product research has shifted from classical forward pharmacology toward reverse pharmacology, an approach that begins with documented traditional use and proceeds through experimental validation to mechanistic elucidation and clinical proof of concept (Patwardhan and Mashelkar, 2009) [6]. This paradigm aligns with the Four Pillars of Best Practice in Ethnopharmacology, which demand rigorous standards across botanical, chemical, pharmacological and ethnopharmacological dimensions (Heinrich et al., 2022) [5]. Because complex plant extracts simultaneously modulate multiple molecular targets, the concepts of polypharmacology (Anighoro et al., 2014) [7] and network pharmacology (Hopkins, 2008) [8] provide the theoretical scaffolding needed to interpret multi-target effects and to design experiments that move beyond descriptive reporting.

Accordingly, the present review aims to: (i) systematically consolidate the botanical, ethnobotanical, phytochemical and pharmacological evidence specifically attributable to *O. cochenillifera*; (ii) critically

evaluate the consistency, methodological rigour and translational relevance of existing preclinical studies; (iii) identify and explain the key theoretical frameworks that contextualize multi-component natural product research; (iv) propose an evidence-based conceptual framework linking traditional knowledge, phytochemical diversity and pharmacological outcomes; and (v) delineate priority research gaps and future directions necessary to advance this species from traditional use toward evidence-based therapeutic application.

2. Theoretical Frameworks Underpinning Ethnopharmacological Research

Three complementary theoretical frameworks were used to structure the analysis in this review, because they jointly explain why whole-plant extracts behave differently from single-molecule drugs and how traditional knowledge can be translated into mechanistic science.

2.1 Reverse Pharmacology

Reverse pharmacology is an approach that starts from documented, experiential traditional use and proceeds backward through experimental validation toward mechanism and clinical proof of concept (Patwardhan and Mashelkar, 2009) [6]. Its principal strength is the reduction of attrition: ethnophototically pre-selected plants are enriched for bioactivity relative to random screening. Its principal risk is the legitimization of tradition without adequate experimental scrutiny; reverse pharmacology is therefore best understood as a hypothesis-generating, rather than hypothesis-confirming, paradigm. In the case of *O. cochenillifera*, the traditional use of cladodes for inflammatory and gastrointestinal complaints provided the direct rationale for the subsequent validation of anti-colic and gastroprotective effects in rodent models (Tavares et al., 2023a, 2023b) [13, 14].

2.2 Polypharmacology

Polypharmacology recognizes that bioactive chemical mixtures, such as plant extracts, exert therapeutic effects through the simultaneous modulation of multiple molecular targets rather than through a single high-affinity interaction (Anighoro et al., 2014) [7]. This concept has two important corollaries for *O. cochenillifera* research. First, the concurrent influence of its phenolic-rich hydroethanolic extract on NF- κ B, MAPK1/ERK2, COX-2 and antioxidant enzyme systems is not experimental noise but the expected signature of a multi-component intervention. Second, activity observed in a whole extract cannot be attributed to any single constituent without bioassay-guided fractionation and testing of isolated compounds, a step that has so far not been completed for this species.

2.3 Network Pharmacology and Systems Pharmacology

Network pharmacology extends polypharmacology by mapping compound-target interactions onto biological networks and asking how a multi-component intervention perturbs the network as a whole (Hopkins, 2008) [8]. Systems pharmacology further integrates multi-omics data and computational modelling (Bai et al., 2024) [22]. Applied to *O. cochenillifera*, this framework predicts that the phenolic acids, isorhamnetin glycoside and putative isoflavones identified in cladode extracts converge on a limited set of hub pathways, including NF- κ B, MAPK and redox-regulatory signalling. This convergence offers a mechanistic explanation for the coherent anti-inflammatory and gastroprotective phenotypes observed in vivo and provides testable hypotheses for future transcriptomic and proteomic validation.

These frameworks are operationalized through the Four Pillars of Best Practice in Ethnopharmacology:

1. botanical rigour (correct identification and voucher specimens);
2. chemical rigour (analytical characterization and dereplication);

3. pharmacological rigour (mechanistically informative assays with appropriate controls); and
4. ethnopharmacological rigour (documented traditional use and ethical considerations) (Heinrich et al., 2022) [5]. Each thematic section below is evaluated against these pillars.

3. Botanical Identity and Taxonomic Considerations

Accurate taxonomic identification constitutes the foundational pillar upon which all subsequent phytochemical and pharmacological conclusions rest (Heinrich et al., 2022) [5]. *Opuntia cochenillifera* (L.) Mill. is classified within Kingdom Plantae, Order Caryophyllales, Family Cactaceae, Subfamily Opuntioideae and Genus *Opuntia* Mill. The species is accepted as *O. cochenillifera* (L.) Mill. by Plants of the World Online, with *Nopalea cochenillifera* (L.) Salm-Dyck designated as its nomenclatural synonym (Royal Botanic Gardens, Kew, 2026) [10]. This clarification carries significant pharmacological implications: several methodologically robust studies of anti-inflammatory and gastroprotective activity were published under the synonym *N. cochenillifera* (Tavares et al., 2023a, 2023b) [13, 14], and failure to recognize this synonymy risks either the omission of relevant evidence or the inappropriate inclusion of data from taxonomically distinct species.

Morphologically, *O. cochenillifera* is a perennial succulent shrub or small tree reaching approximately 4 m in height. It develops a cylindrical, woody, jointed trunk with flattened, green, elliptic to narrowly elliptic cladodes (15 to 40 cm long, 5 to 12 cm broad) that serve as the principal photosynthetic and water-storage organs. The cladodes bear areoles with deciduous glochids; the plant is generally unarmed or nearly spineless, although short spines may occasionally develop on older joints. The leaves are highly reduced, subulate, approximately 3 mm long and soon deciduous. Flowers arise from the cladodes, measure approximately 1.5 cm in diameter and 5 to 6 cm in length, and have a reddish to crimson perianth with stamens extending beyond the perianth. The fruits are characteristically red and may reach approximately 5 cm in length [10]. The cladodes constitute the major plant material investigated for phytochemical, pharmacological and mucilage-related properties, while the fruit has also been evaluated for antimicrobial activity (Suryawanshi and Vidyasagar, 2016) [19]. Accurate morphological identification, preferably supported by authenticated herbarium voucher specimens deposited in recognized herbaria, is essential to ensure that pharmacological findings are correctly attributed to the species and to improve inter-study reproducibility.

4. Ethnobotanical Knowledge and Traditional Uses

Ethnobotanical documentation provides the empirical foundation for reverse pharmacological investigation. Plants of the World Online records *O. cochenillifera* as used for food, animal food, medicine, environmental purposes and as invertebrate food (Royal Botanic Gardens, Kew, 2026) [10]. The succulent, water-rich cladodes constitute the primary plant part consumed and used medicinally across regions where the species is cultivated or naturalized, including Mexico, Brazil, India, Indonesia and the Philippines.

Traditional medicinal applications documented under the synonym *N. cochenillifera* include the management of inflammatory conditions, cholesterol disorders, blood pressure dysregulation, kidney and urinary complaints and diabetes (Tavares et al., 2023b) [14]. In Brazilian traditional medicine the cladodes are specifically employed for their purported anti-inflammatory properties and for gastrointestinal complaints, providing a direct ethnopharmacological rationale for the experimental colitis and gastric injury models subsequently investigated. In the Philippines the mucilaginous stems

have been used for water clarification and topical applications, reflecting an empirical understanding of the mucilage's physicochemical properties (StuartXchange, 2018) [11]. The species has additionally been associated historically with cochineal production, because its cladodes host cochineal insects (*Dactylopius* spp.) from which carminic-acid-based red dye is obtained, contributing to the economic and cultural importance of the species in Mesoamerican and Andean regions.

These traditional indications are scientifically significant because several involve inflammatory, oxidative, metabolic or vascular processes that are amenable to experimental pharmacological investigation. Nevertheless, traditional claims must be interpreted as ethnobotanical observations rather than established clinical efficacy: historical use provides a compelling rationale for scientific inquiry but does not itself demonstrate therapeutic effectiveness, safety, optimal dosage or clinical applicability (Heinrich et al., 2022) [5]. To date, the traditional association of *O. cochenillifera* with inflammatory disorders has received the strongest experimental corroboration, with phenolic-rich extracts attenuating intestinal inflammation and oxidative stress in rodent models (Tavares et al., 2023b) [14].

5. Phytochemical Profile and Bioactive Constituents

The pharmacological potential of *O. cochenillifera* is intrinsically linked to its phytochemical composition, which has been partially characterized by chromatographic and spectroscopic methods. The principal bioactive constituents identified to date comprise phenolic acids, flavonoid glycosides, organic acids and a polysaccharide-rich mucilage fraction (Table 1).

5.1 Phenolic Acids and Flavonoids

Fabela-Illescas et al. (2022) [12] employed high-performance liquid chromatography (HPLC) to quantify six phenolic acids in cladode flour: gallic acid (2708.49 microg/g), ferulic acid (796.73 microg/g), chlorogenic acid (179.70 microg/g), p-coumaric acid (80.58 microg/g), syringic acid (11.12 microg/g) and neochlorogenic acid (9.52 microg/g). The total soluble phenol content was 207.92 mg gallic acid equivalents (GAE)/100 g dry weight (DW), while hydrolysable polyphenols reached 647.99 mg GAE/100 g DW; the flour also contained 3.55 mg/g DW of condensed tannins and 4.36 mg beta-carotene/100 g DW. Antioxidant capacity was confirmed through three complementary assays: DPPH (15.28 mmol Trolox equivalents/g DW), FRAP (20.97 mmol TE/g DW) and ABTS (51.31 mmol TE/g DW) [12].

More comprehensive dereplication was achieved by Tavares et al. (2023a, 2023b) [13, 14] using HPLC-ESI-MSn, which permitted the putative characterization of 25 compounds in hydroethanolic extracts, including saccharides (maltose, sucrose, raffinose), organic acids (gluconic, citric and malic acids), phenolic acids and flavonoids. The total phenolic content of the hydroethanolic extract (NCHE) was 67.85 mg GAE/g dry extract, and the total flavonoid content was 46.16 mg quercetin equivalents/g dry extract; the physicochemical profile revealed high carbohydrate content (67.86 g/100 g), crude fibre (63.85 g/100 g) and protein (16.36 g/100 g), with low lipid content (2.78 g/100 g) and a pH of 4.50 [14]. A particularly noteworthy finding was the identification of isorhamnetin-3-O-(2",3"-O-di-rhamnose)-glucoside as the major polyphenolic peak in the phenolic-rich extract (Tavares et al., 2023a) [13]. This flavonoid glycoside may contribute significantly to the gastroprotective, anti-inflammatory and cytoprotective effects observed in subsequent bioassays, although its individual activity requires confirmation through isolation and direct biological testing. Tavares et al. (2023b) [14] also reported the first dereplication of putative isoflavones in this species based on characteristic MS/MS fragmentation patterns, a significant finding given the near-exclusive distribution of isoflavones within the Fabaceae

family. It must be emphasized, however, that all of these assignments derived from mass-spectrometric fragmentation are putative; none of the flavonoid glycosides has been isolated in pure form and confirmed by nuclear magnetic resonance (NMR) spectroscopy, which represents a critical chemical-standardization gap.

5.2 Polysaccharide-Rich Mucilage

Beyond low-molecular-weight secondary metabolites, *O. cochenillifera* contains substantial quantities of mucilage, a complex polysaccharide-rich material with functional and potential biomedical relevance. Monrroy et al. (2017) [15] reported that mucilage extracted from cladodes contains approximately 40% total carbohydrates, together with proteins and minerals including calcium (predominant), phosphorus, magnesium, iron, potassium, zinc and copper. The mucilage exhibited a water-holding capacity of 2.78 g/g dry mucilage and an oil-holding capacity of 1.80 g/g, alongside emulsifying and stabilizing properties [15]. It is important to note that an erroneous value of 15 g/g for the water-holding capacity of this mucilage appears in some secondary sources; the value of 2.78 g/g reported in the primary study is used consistently throughout this review.

Recent investigations have expanded these characterizations substantially. Monteiro et al. (2025) [16] evaluated the rheological behaviour, cytotoxicity and antioxidant potential of cladode mucilage, reporting satisfactory cellular viability (exceeding 70% in MTT and sulforhodamine B assays) and pseudoplastic (shear-thinning) flow behaviour. Pereira et al. (2025) [17] employed optimized extraction protocols and demonstrated that the mucilage possesses an amorphous structure, thermal stability and high cell viability in RAW 264.7 and HEK 293 cell lines at concentrations exceeding 100 microg/mL. These physicochemical and biocompatibility profiles support the potential application of *O. cochenillifera* mucilage as a biodegradable functional material in pharmaceutical, food, cosmetic and biomedical formulations.

Table 1. Major Bioactive Constituents Identified from *Opuntia cochenillifera*

Compound / Chemical Class	Plant Part / Matrix	Analytical Method	Reported Biological Association	Reference
Gallic acid	Cladode flour	HPLC-DAD	Most abundant phenolic acid; antioxidant (DPPH, FRAP, ABTS)	Fabela-Illescas et al. (2022) [12]
Ferulic acid	Cladode flour	HPLC-DAD	Phenolic constituent; antioxidant	Fabela-Illescas et al. (2022) [12]
Chlorogenic acid	Cladode flour	HPLC-DAD	Phenolic constituent; antioxidant	Fabela-Illescas et al. (2022) [12]
p-Coumaric acid	Cladode flour	HPLC-DAD	Phenolic constituent; antioxidant	Fabela-Illescas et al. (2022) [12]
Syringic acid	Cladode flour	HPLC-DAD	Identified	Fabela-Illescas et

			phenolic constituent	al. (2022) [12]
Neochlorogenic acid	Cladode flour	HPLC-DAD	Identified phenolic constituent	Fabela-Illescas et al. (2022) [12]
Isorhamnetin-3-O-(2,3-O-di-rhamnose)-glucoside	Phenolic-rich hydroethanolic extract	HPLC-ESI-MSn (putative)	Major polyphenolic peak; associated with gastroprotective and antioxidant activity	Tavares et al. (2023a) [13]
Dihydroxybenzoic acid; gluconic, citric, malic acids	Hydroethanolic extract	HPLC-ESI-MSn (putative)	Components of the anti-inflammatory phytocomplex	Tavares et al. (2023b) [14]
Isoflavones (putative)	Hydroethanolic extract	HPLC-ESI-MSn (putative)	First dereplication report for the species	Tavares et al. (2023b) [14]
Polysaccharide-rich mucilage	Cladodes	Gravimetric, FTIR, TGA, DSC, XRD	Functional material; water-holding 2.78 g/g; oil-holding 1.80 g/g	Monrroy et al. (2017) [15]; Monteiro et al. (2025) [16]; Pereira et al. (2025) [17]
Calcium (predominant mineral)	Cladode mucilage	Mineral analysis	Nutritional; potential metabolic relevance	Monrroy et al. (2017) [15]
Phenolic-rich fraction (TPC 67.85 mg GAE/g)	Cladodes	Folin-Ciocalteu; HPLC-ESI-MSn	Anti-inflammatory (IBD model); gastroprotective; antioxidant	Tavares et al. (2023a, 2023b) [13, 14]

6. Pharmacological Activities and Mechanistic Insights

6.1 Anti-Inflammatory Activity: NF-kappaB and MAPK Pathway Modulation

Among the biological activities supported by the most robust species-specific evidence, anti-inflammatory activity stands preeminent. Tavares et al. (2023b) [14] investigated a phenolic-rich hydroethanolic extract of *N. cochenillifera* cladodes in a rat model of 2,4-dinitrobenzenesulfonic acid (DNBS)-induced colitis, administering the extract orally at 100, 200 and 300 mg/kg. Macroscopic analysis revealed that the extract significantly decreased the disease activity index and improved macroscopic and histopathological characteristics of the colon in a dose-dependent manner.

The mechanistic basis for this effect involves specific modulation of the NF-kappaB p65/MAPK signalling axis. DNBS activates the NF-kappaB pathway, increasing nuclear translocation of p65 and the transcription of pro-inflammatory genes including IL-1beta, TNF-alpha and COX-2. The phenolic-rich extract downregulated both gene and protein expression of NF-kappaB p65 in colon tissue and concurrently downregulated MAPK1/ERK2 pathway markers; the extracellular signal-regulated kinase cascade is closely linked with inflammatory bowel disease pathogenesis. At the biochemical level, treatment decreased the pro-inflammatory cytokines interleukin-1beta (IL-1beta) and tumour necrosis factor-alpha (TNF-alpha) while increasing the anti-inflammatory cytokine interleukin-10 (IL-10). Concurrent reductions in malondialdehyde (MDA), a lipid peroxidation marker, and myeloperoxidase (MPO), a neutrophil infiltration marker, indicated attenuation of oxidative stress and neutrophil-associated inflammation. Histopathological and immunohistological analyses demonstrated improved epithelial integrity, including enhanced expression of mucin type 2 (MUC-2) and zonula occludens-1 (ZO-1), tight-junction proteins critical for intestinal barrier function [14].

The compounds implicated in these effects include derivatives of kaempferol and quercetin identified in the extract, together with ferulic acid and gallic acid; gallic acid has been shown to increase IkappaB expression and thereby inhibit NF-kappaB activity, while isoflavones putatively identified in the extract have demonstrated NF-kappaB inhibition in experimental colitis models. The isorhamnetin glycoside, the major polyphenolic peak, may contribute through documented antioxidant and anti-inflammatory properties, although direct evidence for this specific compound in *O. cochenillifera* remains to be established. The convergence of phenolic acids, flavonoids and putative isoflavones on a shared NF-kappaB/MAPK hub is precisely the polypharmacological pattern predicted by network pharmacology (Hopkins, 2008; Anighoro et al., 2014) [7, 8].

The strengths of this study include an authenticated plant source, full extract characterization, a dose-response design and a coherent mechanism. Its limitations include the use of a single acute chemical-induced model, the absence of chronic or genetically driven colitis models, and the reliance on a complex, chemically undefined extract.

6.2 Gastroprotective Activity: Oxidative Stress and Cytokine Modulation

The gastroprotective activity of *O. cochenillifera* was investigated using the same phenolic-rich hydroethanolic extract. Tavares et al. (2023a) [13] evaluated the extract in ethanol- and indomethacin-induced gastric lesion models in rats. Pre-treatment at 100 mg/kg significantly reduced gastric lesions in both models: the protective effect in the ethanol model was highly significant (p less than 0.0001), and in the indomethacin model significant protection was observed at 100 mg/kg (p less than 0.05) and 200 mg/kg (p less than 0.01).

The protective mechanisms were multifactorial. The extract reduced MPO, MDA, TNF-alpha and IL-1beta levels in gastric tissue while increasing glutathione (GSH) and IL-10. Immunohistochemical analysis revealed upregulation of superoxide dismutase (SOD) and downregulation of cyclooxygenase-2 (COX-2). In lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, the extract suppressed reactive oxygen species production without substantial cytotoxicity, as confirmed by MTT assay. Periodic acid-Schiff staining demonstrated restoration of mucus content without modification of gastric juice pH, volume or total acidity. These findings indicate that gastroprotection is mediated through antioxidant, anti-inflammatory and mucus-stimulatory mechanisms rather than through antisecretory activity [13], a mechanistic profile resembling that of gastroprotective flavonoids rather than of proton-pump inhibitors.

6.3 Antimicrobial Activity: Preliminary and Contradictory Evidence

Antimicrobial activity represents one of the earliest experimentally investigated properties of *O. cochenillifera*, yet the evidence remains contradictory and methodologically limited. Suryawanshi and Vidyasagar (2016) [19] evaluated chloroform and methanolic extracts of fruits and cladodes using agar well diffusion against bacterial and fungal organisms. The methanolic extracts exhibited activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida glabrata*, *Candida haemulonii* and *Candida tropicalis* at 40 mg/mL, with comparatively stronger inhibition against *E. coli*, *B. subtilis*, *C. albicans* and *C. glabrata*.

In direct contrast, Silva et al. (2016) [20] investigated crude ethanolic extracts and fractions from large and small cladodes against *S. aureus*, *Staphylococcus epidermidis*, *P. aeruginosa* and *E. coli* and reported no significant antibacterial activity, despite phytochemical screening indicating the presence of phenols, flavonoids, steroids, alkaloids and alkanes. This discrepancy demonstrates that the mere presence of secondary metabolites does not necessarily translate into measurable antimicrobial activity.

Several methodological factors account for these contradictory findings. First, extraction solvent profoundly influences the chemical profile: methanol may extract different constituents than ethanol or chloroform. Second, plant part, geographical origin, cladode maturity and post-harvest processing alter phytochemical composition. Third, differences in test strains, inoculum density and assay format (agar well diffusion versus broth microdilution) limit direct comparability. Fourth, neither study determined minimum inhibitory concentrations (MICs) or minimum bactericidal concentrations according to recognized standards such as those of the Clinical and Laboratory Standards Institute. Consequently, the antimicrobial potential of *O. cochenillifera* should be regarded as preliminary and hypothesis-generating rather than established.

6.4 Antioxidant Activity: Extract- and Assay-Dependent Effects

Antioxidant findings in *O. cochenillifera* have historically been inconsistent. Silva et al. (2016) [20] reported no significant antioxidant activity in crude ethanolic extracts and fractions using the DPPH assay, despite qualitative detection of phenols and flavonoids. Conversely, Fabela-Illescas et al. (2022) [12] documented antioxidant activity in cladode flour using three complementary assays (DPPH, FRAP, ABTS), with the highest activity correlating with polyphenol content. Guerra et al. (2022) [21] detected DPPH radical-scavenging activity in a methanolic extract of fresh cladodes, although ABTS activity was comparatively low, and Monteiro et al. (2025) [16] reported limited protective antioxidant effects of mucilage at the concentrations tested.

These discrepancies are interpretable rather than inexplicable. Antioxidant capacity measured by in vitro radical-scavenging assays reflects only the chemical reactivity of extracted compounds under assay conditions and is strongly dependent on solvent polarity, matrix effects and the specific radical used. The qualitative presence of phenolic compounds cannot therefore be equated with effective antioxidant capacity in vivo, and none of the available studies measured antioxidant effects in intact biological systems beyond cell-based ROS assays [13]. Claims of systemic antioxidant benefit based solely on DPPH or ABTS values should be regarded as unsupported.

6.5 Metabolic and Antihyperglycaemic Effects

Traditional use of *O. cochenillifera* for diabetes management has stimulated experimental investigation of its antihyperglycaemic properties. Guerra et al. (2022) [21] demonstrated that administration of fresh blended cladodes (2 g/kg) attenuated postprandial glycaemia in rats following an oral starch load, with effects comparable to the reference drug acarbose (4 mg/kg). A methanolic extract of the cladodes

contained phenolic compounds and demonstrated DPPH antioxidant activity; however, it did not exhibit marked alpha-glucosidase inhibitory activity, suggesting that the observed antihyperglycaemic effect may involve mechanisms other than direct inhibition of this digestive enzyme.

Several alternative mechanisms remain plausible: delayed gastric emptying attributable to the mucilaginous matrix, modulation of intestinal glucose transporters, or post-absorptive metabolic effects mediated by phenolic compounds. Each hypothesis requires direct experimental confirmation, and the acute, single-dose design of the available study precludes conclusions about sustained glycaemic control or utility in diabetes models. Notably, the positive control acarbose inhibits alpha-glucosidase, so the comparable efficacy of a non-alpha-glucosidase-inhibiting preparation implies a distinct mechanism that, if confirmed, could offer a complementary therapeutic rationale.

6.6 Wound-Healing Potential

Wound healing represents an emerging area of investigation supported by recent preclinical evidence. Saraswati et al. (2025) [18] developed a topical cream formulation from *O. cochenillifera* cladodes and evaluated its efficacy in streptozotocin-induced diabetic BALB/c mice. The cream exhibited acceptable physicochemical properties for topical use (pH 6.44, skin-compatible; adhesion 4.97 s; spreadability 5.10 cm; good homogeneity), and phytochemical screening confirmed flavonoids, tannins, terpenoids and alkaloids.

In incision wound models the cream significantly accelerated wound closure compared with untreated diabetic controls (p less than 0.05); histopathological analysis revealed enhanced re-epithelialization (55.95 plus or minus 58.60 micrometre at day 7) and elevated fibroblast scores (2.32 plus or minus 1.06 versus 1.36 plus or minus 0.48 in negative controls). In burn wound models the cream produced healing comparable to standard therapy by day 14, with accelerated epithelial regeneration and enhanced fibroblast activity. These findings suggest that *O. cochenillifera* enhances fibroblast proliferation, collagen organization and epithelial migration, plausibly mediated by its flavonoid and alkaloid content through modulation of inflammatory signalling and growth factor pathways [18]. The wide standard deviations in histomorphometric measurements, however, indicate substantial inter-animal variability, and the mechanistic attribution remains inferential rather than demonstrated.

6.7 Functional and Biomedical Applications of Mucilage

The mucilage of *O. cochenillifera* represents an important functional component with pharmaceutical, food, cosmetic and biomedical potential. Monrroy et al. (2017) [15] established its carbohydrate, protein and mineral content and its useful water- and oil-holding characteristics. Monteiro et al. (2025) [16] characterized its rheology as pseudoplastic and non-Newtonian with satisfactory cellular viability, and Pereira et al. (2025) [17] demonstrated an amorphous structure, thermal stability and high biocompatibility in mammalian cell models. These findings indicate that the biomedical importance of the species may extend beyond conventional medicinal activity to provide polysaccharide-rich biomaterials suitable for use as excipients, hydrogels, films, wound-dressing materials, stabilizers, emulsifiers or components of controlled-release systems. The principal limitation of this line of research is the absence of in vivo biomaterial performance and biodegradation data.

Table 2. Summary of Species-Specific Pharmacological and Functional Studies on *Opuntia cochenillifera* (L.) Mill.

Study	Plant Material / Extract	Experimental Model / Assay	Key Findings	Limitations
Suryawanshi and Vidyasagar (2016) [19]	Fruit and cladode; chloroform and methanolic extracts	Agar well diffusion against bacteria and fungi	Methanolic extracts active against <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> and <i>Candida</i> spp. at 40 mg/mL	No MIC/MBC determined; qualitative screening only
Silva et al. (2016) [20]	Large and small cladodes; crude ethanolic extracts and fractions	DPPH; antibacterial assay (<i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> , <i>E. coli</i>)	No significant antibacterial or antioxidant activity detected	Crude extracts; possible compound degradation; limited extraction efficiency
Monrroy et al. (2017) [15]	Cladode mucilage	Physicochemical characterization; WHC, OHC, emulsifying capacity	Carbohydrate-rich (approx. 40%); minerals (Ca, P, Mg, Fe, K, Zn, Cu); WHC 2.78 g/g; OHC 1.80 g/g	No direct biological activity tested
Fabela-Illescas et al. (2022) [12]	Cladode flour	HPLC phenolic profiling; DPPH, FRAP, ABTS	Six phenolic acids quantified; antioxidant activity in all three assays	Flour matrix rather than extract; individual compound activities not tested
Guerra et al. (2022) [21]	Fresh cladodes and methanolic extract	Starch load in rats; alpha-glucosidase inhibition; DPPH, ABTS	Attenuated postprandial glycaemia; limited alpha-glucosidase inhibition	Acute study only; mechanism unclear; no diabetic model used
Tavares et al. (2023a) [13]	Cladodes; phenolic-rich hydroethanolic extract (NCHE)	Ethanol- and indomethacin-induced gastric lesions in rats; oxidative stress markers	Reduced gastric lesions; decreased MPO, MDA, TNF-alpha, IL-1beta; increased GSH, IL-10; enhanced healing	Complex extract; active constituent(s) unidentified; single-dose regimen
Tavares et al. (2023b) [14]	Cladodes; hydroethanolic	DNBS-induced colitis in rats	Decreased disease activity index	Animal model only; no clinical

	extract (NCHE)	acute toxicity (2000 mg/kg)	decreased IL-1beta, TNF-alpha; increased IL-10; decreased MDA, MPO; no acute toxicity	translation; extract dose-dependent
Monteiro et al. (2025) [16]	Cladode mucilage	Rheology; MTT and SRB cytotoxicity; antioxidant assays	Pseudoplastic behaviour; satisfactory cellular viability; limited antioxidant effect	No in vivo biomaterial testing; concentration-limited data
Pereira et al. (2025) [17]	Cladodes; optimized mucilage extraction	FTIR, TGA, DSC, XRD, rheology; RAW 264.7 and HEK 293 cell lines	Amorphous structure; thermally stable; pseudoplastic; high cell viability	No functional biomaterial application tested
Saraswati et al. (2025) [18]	Cladode-based cream	STZ-diabetic mice; incision and burn wound models	Accelerated wound closure; enhanced fibroblast activity; organized collagen deposition	Topical formulation only; mechanism not fully elucidated

8. Toxicological Considerations

The safety profile of *O. cochenillifera* has been partially characterized in preclinical models, with available data suggesting a favourable acute safety margin, although comprehensive toxicological evaluation remains incomplete. Tavares et al. (2023b) [14] conducted an acute toxicity study following Organisation for Economic Co-operation and Development (OECD) guidelines, in which a single oral administration of the phenolic-rich hydroethanolic extract at 2000 mg/kg to female Wistar rats produced no mortality and no obvious signs of toxicity during a short observation period (48 hours) or a prolonged period (14 days). Body weight and feed consumption remained unchanged, and Hippocratic screening revealed no treatment-related adverse effects on general behaviour; in the open field test no significant differences in ambulation, rearing or grooming were detected.

Biochemical and haematological analyses further supported the absence of acute toxicity. No significant alterations were observed in glucose, triglycerides, total cholesterol, urea, creatinine, albumin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Haematological parameters, including erythrocyte count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), leukocyte count and platelet count, remained within normal ranges [14]. Cytotoxicity assessments reinforce these findings: the phenolic-rich extract showed no cytotoxicity in RAW 264.7 macrophages at tested concentrations [13]; mucilage cell viability exceeded 70% in MTT and sulforhodamine B assays (Monteiro et al., 2025)

[16]; high viability was observed in RAW 264.7 and HEK 293 cells at concentrations exceeding 100 microg/mL (Pereira et al., 2025) [17]; and no erythema or oedema was observed 24 hours after cream application in animal irritation tests (Saraswati et al., 2025) [18].

Despite these reassuring preliminary data, significant toxicological gaps persist. No subchronic or chronic toxicity studies have been conducted; reproductive toxicity, genotoxicity screening (for example, Ames test and micronucleus assay) and pharmacokinetic or bioavailability profiling are absent from the literature; and the potential for herb-drug interactions, particularly with antidiabetic, antihypertensive or anti-inflammatory medications, has not been investigated. Until such data become available, therapeutic claims regarding long-term safety should be appropriately hedged.

7. Future Perspectives

Table 3 summarizes the principal gaps and corresponding priorities. In brief, future investigations should prioritize: taxonomically authenticated material with deposited voucher specimens and reported collection coordinates; chemically standardized extracts with defined total phenolic and flavonoid content and HPLC-MS profiles used consistently across studies; bioassay-guided fractionation coupled with preparative chromatography and high-resolution NMR to isolate and identify the compounds responsible for the anti-inflammatory and gastroprotective activities; network-pharmacology predictions of multi-target interactions validated experimentally through transcriptomics or proteomics; chronic disease models, including repeated dextran sulfate sodium colitis and streptozotocin-induced diabetes, rather than acute challenge models alone; comprehensive toxicological packages encompassing subchronic toxicity, genotoxicity and pharmacokinetic studies; systematic evaluation of mucilage in wound-healing formulations, edible films and controlled-release matrices with crosslinking strategies and in vivo biodegradation kinetics; and, ultimately, randomized controlled clinical trials for the most plausible indications, most notably functional dyspepsia, mild inflammatory bowel conditions and topical wound care, using standardized extracts with established chemical markers.

Table 3. Principal Research Gaps and Priority Future Directions for *Opuntia cochenillifera*

Domain	Identified Gap	Priority Future Direction
Botanical	Taxonomic confusion between <i>O. cochenillifera</i> and <i>N. cochenillifera</i> ; frequent absence of voucher specimens	Mandatory voucher deposition and nomenclatural reconciliation in all future studies
Chemical	No isolated, NMR-confirmed bioactive compounds; MS-based assignments remain putative	Bioassay-guided fractionation with preparative chromatography and structure confirmation
Pharmacological	Contradictory antimicrobial/antioxidant data; reliance on acute single-dose models	Standardized extracts tested across laboratories, models and seasons; chronic disease models
Mechanistic	Attribution of effects to whole extracts only	Network-pharmacology-guided target validation using transcriptomics/proteomics

Toxicological	Only acute toxicity data available; no genotoxicity, reproductive or pharmacokinetic studies	Full OECD-compliant toxicological package and bioavailability profiling
Translational	No clinical trials; biomaterial applications untested in vivo	Phase I/II trials for dyspepsia, mild IBD and wound care; in vivo biomaterial evaluation

8. Conclusion

Opuntia cochenillifera (L.) Mill. constitutes a promising yet comparatively underexplored source of bioactive natural products and functional biomaterials within the Cactaceae. The available preclinical evidence, though limited in volume and heterogeneous in methodology, converges on several biologically plausible activities that align with traditional ethnopharmacological use. Phenolic-rich extracts have demonstrated reproducible anti-inflammatory effects in rodent colitis models through downregulation of NF-kappaB p65 and MAPK1/ERK2 signalling, reduction of IL-1beta and TNF-alpha, elevation of IL-10, and attenuation of MDA and MPO; gastroprotective activity has been corroborated in independent models of ethanol- and indomethacin-induced gastric injury; and the polysaccharide-rich mucilage exhibits favourable physicochemical properties and excellent biocompatibility that render it suitable for biomedical material development.

Nevertheless, significant knowledge gaps constrain translational value. Antimicrobial and antioxidant findings remain inconsistent across studies and appear highly dependent on extraction solvent, plant part, geographical origin and assay methodology. No clinical trials have been conducted, and the active constituents responsible for the most promising effects, particularly the isorhamnetin glycoside and specific phenolic acid fractions, have not been isolated or independently validated in purified form. The species thus remains situated in a preclinical valley: sufficiently interesting to justify continued research, yet insufficiently characterized to support therapeutic recommendations.

By embracing the frameworks of reverse pharmacology, polypharmacology and network pharmacology, and by adhering to the Four Pillars of Best Practice in Ethnopharmacology, future research can move from descriptive reporting toward mechanistic understanding, chemical standardization and evidence-based application. The conceptual framework proposed here provides a structured roadmap for this journey, emphasizing that only through systematic investigation can *O. cochenillifera* advance from a historically important ethnobotanical resource to a clinically validated therapeutic agent or functional biomaterial.

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