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Original Article

A Review on the Bioactive Spectrum of Opuntia Ficus-Indica and its Translational Potential in Oral Oncology

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Abstract - Roughly, most of all clinically approved cancer chemotherapeutics have direct or structural analogy, their origin in natural products, thus underlining the continued importance of botanical pharmacology. In this vast field, the species Opuntia ficus-indica or nopal cactus deserves particular interest, as it is one of the few edible plant species with millennia-long exposure to human diets, a chemically diverse secondary metabolome, and adaptability to environments where conventional food crops do not survive. As an adapted species to extreme conditions of arid climates, Opuntia ficus-indica possesses crassulacean acid metabolism, water storage tissue with mucilage, and a multilayer defense system to cope with long-term drought. The same biochemical pathways responsible for these survival adaptations also underlie the species' pharmacologically interesting secondary metabolites, including flavonoids, phenolic acids, nitrogen-containing betalains, sterols, polyunsaturated fatty acids, vitamins, and high-molecular-weight mucilage polysaccharides, each with unique biological activities, which have increasingly captured the interest of experimental investigations. Scientific interest in this plant has expanded considerably since the early 2000s. Studies now report anticancer activity, anti-inflammatory responses, neuroprotection, antimicrobial effects, and metabolic benefits, all from different fractions, different plant organs, and often different species of Opuntia. However, it is harder to find work specifically addressing the oral cavity. And that is the central puzzle this review is concerned about. OSCC kills approximately. 145,000 people annually, the oral mucosa is the first tissue any ingested phytochemicals reach. Yet the published literature barely asks what happens at that interface. Despite O. ficus-indica's direct mucosal contact during ingestion and despite oral squamous cell carcinoma ranking among the ten most common cancers worldwide, the oral cavity has attracted minimal attention as a site of investigation among researchers. This disconnect is the central concern motivating the present review. Three aims structure the analysis that follows: a critical synthesis of the phytochemical diversity documented for O. ficus-indica; an appraisal of the mechanistic and in-vivo anticancer evidence, including an honest accounting of its limitations; and the construction of a translational argument for purpose-designed investigation of chemopreventive activity in OSCC models.

Keywords - OSCC, Cancer, Ficus-Indica, CAM.

1. Introduction

Cancer does not distribute itself randomly across populations. Incidence tracks closely with industrialisation, rising in tandem with changes in diet, pollution exposure, and the kind of chronic low-grade inflammatory burden that seems almost inseparable from modern life [1]. Palaeontological evidence is instructive here—mummified tissue and skeletal remains from pre-industrial populations show neoplastic change at rates substantially lower than those seen today, which at minimum suggests the disease is not simply an inevitable consequence of aging [2]. Current treatment relies heavily on cytotoxic chemotherapy, a modality that works, often dramatically, but that also produces well-documented haematological, gastrointestinal, and peripheral nerve toxicities that significantly compromise patient wellbeing [3]. There is genuine clinical rationale, then, for identifying plant-derived agents capable of reducing cancer risk at earlier stages, before the tumour is established and before systemic treatment becomes necessary [3].

Oxidative stress sits near the centre of most mechanistic accounts of carcinogenesis. ROS at physiological concentrations do normal and necessary things; they function as second messengers, regulate kinase cascades, and participate in innate immune signalling. The problem begins when their production becomes chronic and overwhelming, as happens under sustained tobacco carcinogen exposure, during mitochondrial dysfunction, or in the inflammatory microenvironment surrounding pre-malignant tissue. At that point, DNA strand breaks accumulate, lipid peroxidation products modify protein function, and NF-κB-driven transcriptional reprogramming shifts cells toward a proliferative phenotype [4-6]. Dietary antioxidants that can intervene in this process by activating Nrf2-dependent response elements, chelating redox-active iron and copper, or simply competing with biomolecular targets for radical intermediates, are attractive precisely because they do so chronically and at low concentrations, which is the pharmacological logic of chemoprevention rather than treatment [5, 7]. Cacti could grow in full sun, degraded soils, can handle temperature swings of 40°C or more, and can survive without rain. Meeting these conditions requires a sophisticated internal antioxidant system, along with the secondary metabolites that sustain it: flavone and flavonol glycosides, hydroxycinnamic acids, nitrogen-bearing betalain pigments, carotenoids, tocopherols, and arabinogalactan polysaccharides. These are also the ones that show up consistently in pharmacological assays [8-11]. Opuntia ficus-indica (nopal cactus) accumulates quercetin-3-glucoside, quercetin-3-rutinoside, betanin, and indicaxanthin, and many other bioactive components in its cladodes and fruit. The radical-scavenging rate constants of these compounds, measured by stopped-flow spectrophotometry, exceed that of ascorbate under specific conditions, which act as a meaningful benchmark, given vitamin C's established biological antioxidant role [12-14]. Cells pre-treated with cactus pear extracts also show upregulated glutathione peroxidase and catalase activity, suggesting that extracts trigger the enzyme-level defenses beyond simple radical capture [12, 14].

At the preclinical level, extracts and isolated constituents of O. ficus-indica show measurable activity across at least six tumour type categories: colorectal, breast, prostate, gastric, hepatic, and haematological [15-18]. Mechanistically, reduced tumour cell viability in these systems is more often relevant to redox-mediated pathway modulation, i.e., caspase activation, Bcl-2 family protein rebalancing, NF-κB attenuation, and not to the frank membrane disruption characteristic of cytotoxic drugs [19, 20]. This distinction matters clinically in that a mechanism rooted in regulatory pathway correction rather than indiscriminate cytotoxicity implies a lower probability of off-target toxicity and positions cactus-derived preparations more naturally within the chemoprevention paradigm [19, 20].

A striking omission runs through the entire published corpus, despite the plant being consumed orally, almost no study examines its effects on O. ficus-indica directly exposed to ingested phytochemicals, namely the oral mucosa. Oral epithelium faces a uniquely hostile redox environment caused by continuous exposure to tobacco nitrosamines, ethanol-derived acetaldehyde, polymicrobial biofilm oxidants, and the acidity of dietary contents, all recognised risk factors for OSCC [4, 6, 8]. The corresponding absence of data on the mucosal antioxidant effects of O. ficus-indica is therefore doubly puzzling. Moreover, because O. ficus-indica's phytochemicals contact the oral mucosa before reaching any systemic compartment, this tissue should, in principle, be the first and most highly exposed target.

Against this backdrop, the present review pursues three specific aims, i.e., synthesising phytochemical and mechanistic data on anticancer activity across existing experimental models; critically evaluating the robustness of the reported findings; and making an explicit translational case for targeted OSCC investigation. The mechanistic actions of Opuntia ficus-indica in cancer systems are elaborated in sections 3.1–3.4. It is the authors' contention that a focused, well-powered experimental program in an oral epithelial model guided by the mechanistic precedents assembled is both scientifically justified and methodologically achievable. Commentary on the translational role of O. ficus-indica is woven throughout the mechanistic and gap analyses that follow.

2. Taxonomy, Distribution, and Botanical Characteristics of Opuntia Ficus-Indica

2.1. Taxonomy and Systematic Classification

Classified within the order Caryophyllales and the family Cactaceae, Opuntia ficus-indica (L.) Mill. is simultaneously the most economically important and taxonomically contentious member of its genus [21]. Rampant hybridisation, allopolyploidisation, and environmentally driven phenotypic plasticity have historically confounded species delimitation across Opuntia ficus-indica itself, which is now understood to represent a domesticated derivative of wild Mexican progenitors rather than a species with a single natural origin [8, 21, 23]. Morphological evidence for this domestication includes the reduction of armature (glochid and spine density), the enlargement of reproductive structures, and the selection of palatable, low-oxalate cladode tissue [21, 23].

2.2. Geographic Distribution and Ecological Adaptation

Commercial production of nopal cactus is documented across the Mediterranean littoral, the Ethiopian and Maghreb highlands, arid zones of South Africa, north-western India, the Chilean Atacama fringe, and the south-western United States, and more. A distribution that reflects the plant is astonishingly edaphic and climatic, with tolerance as a feature [22, 23, 25]. At the heart of this tolerance lies CAM photosynthesis, which is a mechanism of opening stomata only at night, when vapour pressure deficits are low. O. ficus-indica achieves water-use efficiencies of 25–50 kg biomass per cubic metre of water. The values are several-fold higher than C3 cereals [22, 26]. When precipitation is scarce and soils are nutrient-poor, cladode parenchyma simultaneously acts as a capacitor, storing water sufficient to sustain metabolic activity through weeks of drought [26, 30]. These traits position this species as a candidate for productive land use on terrain that would otherwise support little or no agriculture, an argument gaining renewed traction in the context of accelerating desertification [25, 30].

2.3. Morphological and Anatomical Features

The most pharmacologically studied organs of O. ficus-indica are the cladodes, which are succulent, photosynthetically active stem segments whose parenchymatous interior contains up to 95% water, sequestered within mucilage polymers [22, 23, 29]. Structurally, mucilage in the cladode parenchyma consists of arabinose- and galactose-rich heteropolysaccharides, which cross-link through calcium bridges, that imbue the tissue with the gel-forming, hydrocolloid properties exploited in food and pharmaceutical applications in recent days [27, 28]. A waxy cuticle several micrometres thick overlies the epidermis, limiting cuticular transpiration at negligible rates [29]. Flower structures, even though less studied, are now attracting interest as sources of flavonoid-rich fractions with proven cytostatic properties [8, 27]. Fruit pulp colour ranges from ivory to deep crimson, reflecting betacyanin & betaxanthin ratios that vary substantially by cultivar and photoperiod, creating natural variation in antioxidant pigment content that complicates cross-study comparisons [8, 27]. Seed oil, cold-pressed or Soxhlet-extracted, is rich in linoleic acid (45–63% of total fatty acids) and γ-tocopherol, attracting cosmetic and nutraceutical interest independently of the cladode fraction [8, 23, 34].

2.4. Physiology and Stress-Related Biochemistry: Crassulacean Acid Metabolism (CAM)

CAM systems do not just manage water. The nocturnal carbon fixation cycle and the enzymatic reconfiguration it requires appear to sustain constitutive expression of antioxidant enzymes and superoxide dismutase, ascorbate peroxidase, and catalase that drive continuous phenolic and betalain biosynthesis through the diurnal cycle [8, 29, 32]. At peak UV irradiance, when stomata are fully closed and photochemical damage is greatest, the plant depends entirely on this internal network to neutralise the photo-oxidative radical production [8, 31, 34]. Which means, practically, that O. ficus-indica is not a plant that happens to contain antioxidant compounds alongside other metabolic products. It is a plant under permanent oxidative pressure that has evolved to produce these compounds at high levels as a condition of survival. That is a meaningfully different starting point for pharmacological investigation. Compositional data from cladode and mucilage fractions are consistent with this interpretation, reporting wound-repair effects, cytokine suppression, and mucosal barrier protection attributable to polysaccharide and polyphenol fractions whose structural complexity likely reflects the selective demands of stress-driven biosynthesis [27, 28, 32].

Table 1. Bioactive Constituents of *Opuntia ficus-indica*

Category	Bioactive Components	Quantity (per 100 g FW/DW)	Function	Method	References
Flavonoids	Quercetin, kaempferol, isorhamnetin glycosides, isoquercetin, nicotiflorin, narcissin	4-50 mg QE/100g FW; quercetin 4.32 mg; kaempferol 0.22 mg; nicotiflorin 146.5 mg; Narcissin 137.1 mg	Antioxidant, anti-inflammatory, mitochondrial apoptosis support, NF-κB/MAPK modulation	Hydroethanolic/methanol-water extraction with hydrolysis; HPLC-DAD/UHPLC-ESI-MS	36,37,38
Phenolic acids	Gallic acid, caffeic acid, ferulic acid	5-20 mg GAE	Genomic protection from ROS, anti-mutagenic, and radical scavenging	Hydroethanolic extraction; Folin-Ciocalteu and HPLC-DAD/LC-MS	36,39
Betalains	Betanin, indicaxanthin, betacyanins, betaxanthins	5.5-80 mg/100g FW	ROS control, COX-2 suppression, lipid peroxidation reduction	Aqueous/ethanol extracts; UV-Vis + HPLC-DAD	36,40
Seed lipids	β-sitosterol, campesterol	10-50 mg	Cholesterol-linked TME signaling, membrane stability	Hexane Soxhlet or cold press; GC-MS/GC-FID	36,41
Fatty acids	Linoleic, oleic, and palmitic acids	45-63%,16-28%,11-17% total FA	Inflammation modulation, membrane fluidity effects	Seed oil extraction with FAME; GC-FID	36,42

Vitamins	Vitamin C, β-carotene, B complex	10-40 mg,0.5-1.5 mg, detected	Antioxidant cofactors, epithelial resilience	Aqueous/EtOH extraction; HPLC	37,38
Minerals	Ca, Mg, K, Fe, Zn, P	200-500,50-100,100-300,0.5-5 mg	Enzymatic catalysis, mucosa homeostasis	Wet digestion; AAS/ICP	36,43
Amino acids	Proline, arginine, glutamine, threonine.	0.2-1.5 g	Cellular repair, nitrogen metabolism	6N HCl hydrolysis; HPLC/AA analyzer	36,38,44
Mucilage	Cladode & peel mucilage	1-3 g; 10-22% DW	Toxin binding, hydrocolloid barrier	Hot water extraction + EtOH precipitation; HPLC sugars	38,47,48
Composite activity	Total antioxidant capacity	20-80 mg TE	Redox restoration	ABTS/DPPH/FRAP/ORAC assays	36,37,40,41,43,44

3. Mechanistic Relevance of Bioactive Components to Anticancer Activity

The mechanistic literature on O. ficus-indica and cancer is dominated by four compound classes: the nitrogen-containing betalain pigments betanin and indicaxanthin; the flavonols quercetin, kaempferol, and their isorhamnetin glycoside conjugates; the hydroxycinnamic and hydroxybenzoic phenolic acids; and, to some extent, polysaccharides derived from cladodes and seed sterols [35, 37, 39, 42, 47]. Experimental evidence is drawn exclusively from colorectal, breast, hepatic, and melanoma cell and animal models. OSCC data are, by contrast, sparse to the point of constituting a genuine gap [35, 40, 46].

3.1. Redox Modulation and Oxidative Stress–Linked Pathways

Among the redox-active constituents of cactus pear, betanin and indicaxanthin have been studied most intensively. Both compounds exhibit high DPPH and ABTS radical-scavenging activity in the cell-free assays, with indicaxanthin demonstrating pronounced ferric-reducing capacity consistent with electron donation rather than hydrogen-atom transfer as the primary quenching mechanism [37, 38]. In intact cell systems, pre-treatment with betalain-containing fractions initiates oxidative haemolysis, reduces 8-hydroxy-2′-deoxyguanosine formation following tert-butyl hydroperoxide challenge, and also preserves mitochondrial membrane integrity under pro-oxidant conditions [37, 38]. Tesoriere et al. translated these cell-based observations into a controlled dietary intervention: over 28 days, healthy adults consuming 500 g of cactus pear daily recorded lower plasma malondialdehyde, reduced erythrocyte lipid peroxidation, and higher glutathione concentrations relative to an isoenergetic vitamin C comparator group [39]. That dietary betalains can also shift systemic redox parameters measurably within a month of regular consumption is one of the few in-vivo datapoints supporting the translational plausibility of OFI as a chemopreventive dietary agent.

Cladode-derived fractions add a further redox-active dimension. Because the extraction conditions substantially influence phenolic yield, which is a hydroethanolic solvent recovering flavonol glycosides and phenolic acids, it is considered to be more efficient than aqueous systems. The reported total antioxidant capacities span a wide range, i.e., 20-80 mg Trolox equivalents per 100 g fresh weight, even within the same cultivar [35, 37, 45]. This methodological heterogeneity is not a trivial detail: it limits cross-study inference and is one reason why translating in-vitro antioxidant data to dosimetric recommendations remains premature.

Whether O. ficus-indica constituents act as antioxidants or pro-oxidants depends critically on cellular context, in a nuance that carries practical importance for chemoprevention research. Methanolic flower extracts reduced MCF-7 and HepG2 cell viability in concentration ranges that left normal cell lines largely unaffected. This differential cytotoxicity correlates with elevated intracellular ROS, which collapses mitochondrial membrane potential and downstream caspase engagement, with network pharmacology pointing to PI3K–Akt and MAPK as the primary upstream nodes [41]. The apparent paradox is that an extract that scavenges radicals in healthy tissue that also amplifies them in tumour cells and resolves when one considers that cancer cells typically operate with elevated basal ROS and compromised antioxidant reserve. Under these conditions, even modest additional oxidant load can overwhelm buffering capacity and tip the balance toward apoptosis [40, 46].

Taken as a whole, cactus-derived phytochemicals clearly engage redox-sensitive nodes across multiple experimental systems. However, these engagements are pharmacologically meaningful at concentrations achievable in human tissue after oral consumption, which has been almost bypassed. Studies employing short exposure windows (24–72 hours), supra-physiological concentrations, and minimally characterised crude extracts dominate the literature [35, 40, 46]. Until these methodological issues are corrected by exposure protocols that accurately reflect realistic dietary intake and extraction methods that yield standardized, analytically validated preparations, the translational significance of redox data from O. ficus-indica studies remains undetermined.

3.2. Apoptosis and Cell-Cycle Regulation

Intrinsic apoptosis induction is the most frequently documented mechanistic endpoint in O. ficus-indica cancer research, and the convergence across independent reports is notable. Caspases-3 and caspase-9 cleavage, cytochrome-c release from the intermembrane space, Bcl-2 downregulation with reciprocal Bax upregulation, and cell-cycle stalling at G0/G1 or, less frequently, G2/M are all identifiable downstream signatures of betanin-enriched fruit fractions, quercetin-dominant cladode extracts, or isorhamnetin glycoside preparations. [35, 40, 46]. A convergent targeting of shared upstream regulatory nodes rather than a single compound–receptor interaction is shown by the integration of different extract types on the same mitochondrial apoptotic pathway via structurally distinct input ligands. The whole-plant preparations' multi-compound, multi-target reasoning is consistent with this mechanistic framework.

Betalain-rich fruit preparations recapitulate the mitochondrial apoptosis at the cellular level, reducing tumour proliferation indices in a manner consistent with the ROS amplifying and membrane depolarising activities described in cell-free assays [37, 38]. Cladode and flower fractions produce qualitatively similar outcomes across breast, hepatic, and colorectal cell lines [38]. The interpretation is that most studies report outcomes for crude or semi-purified extracts containing dozens of co-occurring metabolites; whether observed cytostatic activity is attributable to a dominant constituent or emerges from additive or synergistic interaction among minor components has seldom been resolved experimentally [38].

The compound-level mechanistic study in an oral cancer model centres on opuntiol, isolated from O. ficus-indica cladodes [18]. Against KB oral carcinoma cells, opuntiol produced an IC_{50} of approximately 30 μM, a value not different from those reported for some established cytotoxics under equivalent assay conditions. Increased intracellular DCFH-DA oxidation (a sign of ROS accumulation), decreased JC-1 red: green fluorescence ratio (a sign of mitochondrial membrane depolarization), and increased cleaved-caspase signals consistent with intrinsic pathway engagement were all found through mechanistic characterization using fluorescence probes and immunoblotting [18]. Additionally, normal lymphocyte viability was maintained at a comparable concentration, indicating a level of selectivity that would greatly support the translational argument if verified in matched oral epithelial controls. The fact that a single structurally defined O. ficus-indica metabolite produces this profile in an oral carcinoma cell line is the strongest site-specific mechanistic evidence currently available and was generated over five years ago without subsequent follow-up in more relevant OSCC lines (CAL-27, HSC-2, SCC-25) or three-dimensional organotypic models.

A systemic caveat applies to every apoptosis study in this literature. Two-dimensional monolayer culture is known to underestimate the dose required for biological effect relative to three-dimensional or in vivo tumour models, partly because monolayer cells lack the hypoxic gradients and stromal interactions that modulate drug sensitivity. When the concentrations used in published OFI studies are back-calculated against known oral bioavailability data for quercetin and betanin, the intestinal absorption of 1–3% for intact betanin, which is higher for aglycone quercetin, the gap between the effective in-vitro dose and what is achievable in mucosal tissue after dietary exposure becomes wide [35, 40, 46].

3.3. Inflammation, Adhesion, and Tumour Micro-Environment

NF-κB activation, COX-2-mediated prostaglandin synthesis, ICAM-1-driven leukocyte adhesion, and VEGF-dependent angiogenesis are interdigitating circuits that drive tumor-associated inflammation. Disrupting any of these nodes could change the microenvironmental conditions that support tumor growth. At concentrations in the low micromolar range, betanin suppresses endothelial ICAM-1 expression, which attenuates monocyte adherence and the ensuing pro-tumoral cytokine release without the COX inhibitors' widespread anti-inflammatory potency and related immunosuppression [36]. This selectivity for an adhesion-signalling target, rather than broad enzymatic blockade, is pharmacologically significant. COX-2 suppression, iNOS inhibition, reductions in TNF-α and IL-6 secretion, and protection of gastrointestinal mucosal barrier integrity have been documented for cladode polysaccharide fractions and polyphenol-rich hydroethanolic extracts across metabolic and inflammatory injury models [37, 38, 42, 45].

The leap from measuring IL-6 in a lipopolysaccharide-stimulated macrophage cell line to making a claim about tumour microenvironment remodelling is considerable, and most O. ficus-indica inflammation studies do not bridge it. Immune cell infiltration dynamics, angiogenic switch timing, and cancer-associated fibroblast contractility, which is the endpoint of most predictive clinical outcomes, are essentially absent from the O. ficus-indica literature [40, 46]. The distinctive features of the oral mucosal immune environment, such as resident macrophage and dendritic cell populations, salivary immunoglobulin A, microbiome-derived short-chain fatty acids that modulate mucosal T-cell polarization, and a physical barrier that is frequently divided by mechanical, thermal, and chemical insults, exacerbate the deficiency for oral cancer in specific There is a significant analytical gap between what has been measured and what is relevant to OSCC biology because none of these factors have been included in O. ficus-indica anti-inflammatory research.

4. Conclusion

Several observations can be stated with reasonable confidence on the basis of published evidence. Nopal cactus accumulates a structurally diverse secondary metabolome of betalain chromoalkaloids, flavonol glycosides, hydroxycinnamic acids, arabinogalactan polysaccharides, and tocopherol-rich seed oils, whose constituents are unevenly distributed across cladode, fruit, flower, and seed compartments [35, 37, 38, 42, 45]. In vitro, these constituents interact with oncologically relevant molecular targets by scavenging ROS and activating antioxidant response elements, depolarising mitochondria, and engaging caspases, downregulating Bcl-2 while upregulating Bax, suppressing ICAM-1 and COX-2, and at least one oral carcinoma model produces selective antiproliferative activity at low micromolar concentrations [35, 37-38, 42, 40-46]. A controlled human trial further confirms that the dietary consumption of cactus pear fruit shifts measurable systemic antioxidant and lipid peroxidation markers [39, 45]. The limitations are equally clear. Two-dimensional monolayer assays at supra-physiological concentrations produce data that frequently fail to replicate in more complex biological systems; crude extracts of uncharacterised composition confound mechanistic attribution; and selectivity index determinations are required side-by-side to test cancerous and matched normal cells are inconsistent [35, 38, 40, 46]. On the pharmacokinetic side, betanin oral bioavailability in humans rarely exceeds 2–3% under conventional dietary conditions, raising legitimate questions about whether the concentration effective in cell culture could ever be sustained in target tissues [35, 41, 45, 46]. For OSCC research, the opuntiol–KB study stands essentially, for which no published work has placed a whole O. ficus-indica preparation, i.e., cladode extract, fruit fraction, or purified compound mixture against primary OSCC lines, patient-derived organoids, or an animal oral carcinogenesis model [16, 18, 40, 46].

None of these limitations should be read as evidence that the hypothesis is wrong; only that it has not yet been tested in the right experimental system. The consistency of findings across unrelated cancer types, the demonstrable in-vivo antioxidant activity at dietary doses, and the existence of at least one structurally defined OFI metabolite active in an oral carcinoma cell line together make a coherent case for targeted study. The field required now is a sequential, hypothesis-driven work. If this program is executed with the methodological discipline that earlier work has often limited, it will be possible to give a definitive answer, affirmative or otherwise, to the question of whether nopal cactus can play a meaningful chemopreventive role in OSCC [35, 37, 38, 40, 42, 46].

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

During the preparation of this work, the author(s) used ClaudeAI in order to rephrase. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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