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Herbal Phytochemicals as Molecular Modulators of Oral Submucous Fibrosis: A Narrative Review of Mechanisms, Clinical Evidence, and Priorities for South Asian Research

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Abstract

Oral submucous fibrosis (OSF) is a chronic, potentially malignant disorder driven mainly by areca nut chewing, common across South Asia, including Pakistan. Research has increasingly mapped the molecular pathways underlying OSF, while a growing body of work has tested plant-derived compounds such as curcumin, lycopene, EGCG and astaxanthin against these same targets. The objective of this study was to bring together the molecular pathogenesis of OSF and the phytochemical approach to treatment, matching compounds to molecular targets with attention to research gaps in Pakistan and other high-burden settings. Review of literature was conducted on studies published between 2012 and 2026 using PubMed, Google Scholar, and ScienceDirect, focusing on molecular mechanism studies, randomised controlled trials, and reviews addressing herbal or nutraceutical compounds in OSF. Curcumin, lycopene, EGCG and astaxanthin produce measurable clinical benefit in OSF through suppression of TGF-β1/Smad signalling, reduced CTGF, and antioxidant activity. Key gaps remain; most trials measure symptoms rather than molecular endpoints, bioavailability is a practical barrier, and oral microbial dysbiosis in OSF is largely untouched by phytochemical research. Locally conducted research accounting for the genetic and exposure profile of Pakistani patients represents a clear and timely priority.

Keywords

Oral submucous fibrosis; phytochemicals; curcumin; lycopene; astaxanthin; TGF-β1/Smad signalling; areca nut; naswar; potentially malignant oral disorder; oxidative stress; microRNA; Pakistan.

1. Introduction

Oral submucous fibrosis (OSF) is a slowly progressing disease of the oral mucosa. It causes stiffening of the cheeks and lining of the mouth, a burning sensation with spicy food, and, over time, a steadily narrowing ability to open the mouth. The World Health Organization has estimated that more than five million people live with OSF, most of them in India, but also in Taiwan, China, and across South Asia (Shih et al., 2019). The disease matters clinically because it is a potentially malignant condition; between roughly 1.5 to 7.6% of OSF cases eventually progress to oral squamous cell carcinoma (OSCC), which gives real practical weight to early, non-surgical management (Shih et al., 2019).

The single strongest cause of OSF is habitual chewing of areca nut, usually as part of betel quid, gutka, or paan, sometimes combined with tobacco (Shih et al., 2019; Pant et al., 2015). In Pakistan and Afghanistan, a related but distinct smokeless tobacco product called naswar, a dipping tobacco mixed with slaked lime and ash, is also strongly linked to oral mucosal disease and oral cancer (Khan et al., 2019). Because these habits are woven into everyday social life across much of South

Asia, OSF is not a rare curiosity confined to textbooks; it is a recurring presence in dental clinics across the region, including in Pakistan.

Treatment of OSF has traditionally relied on corticosteroid injections, hyaluronidase, physiotherapy, and, in advanced cases, surgery. None of these approaches reliably reverse fibrosis entirely, and injections are often painful and poorly tolerated (Shih et al., 2019; Shen et al., 2020). This gap has pushed researchers toward natural compounds already known for antioxidant and anti-inflammatory activity, particularly curcumin from turmeric, (She & Xu, 2024) lycopene from tomatoes (Shafe et al., 2024) and, more recently, astaxanthin, a carotenoid pigment (Chang & Xiong, 2020).

This review has two aims. First, it sets out, in plain terms, the main molecular events that drive OSF, from TGF-β1 to disturbance of the oral microbial community. Second, it maps specific phytochemicals onto these specific targets, drawing on clinical trials and laboratory evidence published mainly between 2012 and 2026. The review then closes by pointing to gaps that a molecular biology-trained dental researcher, particularly one working in Pakistan, is well placed to address.

2. Methods

2.1 Literature Review

A search of PubMed/MEDLINE, Google Scholar, and ScienceDirect was conducted, covering publications from 2012 to 2026. Search terms included, individually and in combination: oral submucous fibrosis, OSF, phytochemicals, herbal, curcumin, lycopene, astaxanthin, EGCG, epigallocatechin gallate, TGF-beta, TGF-β1, Smad signalling, fibrosis molecular mechanism, areca nut, arecoline, oral microbiome, non-coding RNA, lncRNA, miRNA, Pakistan, naswar, and South Asia.

2.2 Inclusion criteria

Studies were included if they: (i) examined molecular mechanisms of OSF pathogenesis in cell, animal, or human tissue models; (ii) reported clinical outcomes of phytochemical or nutraceutical interventions in OSF patients, including randomised controlled trials, controlled trials, or systematic reviews; (iii) addressed epidemiological or genetic aspects of OSF relevant to Pakistan or South Asia; or (iv) reported bioavailability or drug delivery strategies for phytochemicals relevant to OSF.

2.3 Exclusion criteria

Studies were excluded if they were: case reports or case series with fewer than ten patients; conference abstracts without full-text data; studies examining surgical or pharmacological (non-phytochemical) interventions exclusively; or studies published in languages other than English without an available English translation.

2.4 Study selection and synthesis

Titles and abstracts were screened by the author, followed by full-text review of eligible studies. Where high-quality systematic reviews and meta-analyses were available (e.g for curcumin), these were preferentially cited over individual trials.

3. The Molecular Cascade Behind Oral Submucous Fibrosis

3.1 TGF-β1 signalling: the central driver

Arecoline, the principal alkaloid in areca nut, together with polyphenols and slaked lime present in betel quid interferes with extracellular matrix homeostasis in oral tissues, and triggers oral epithelial cells to release TGF-β1. TGF-β1 then binds its receptor on fibroblasts and activates Smad2 and Smad3, which move into the nucleus and switch on genes for type I and type III collagen (Shih et al., 2019; Pant et al., 2015; I. Khan et al., 2012). Areca nut components also activate Smad2 directly in epithelial cells and induce THBS1, a protein that converts latent TGF-β1 into its active form, creating a self-reinforcing loop between epithelium and connective tissue (I. Khan et al., 2012). Additionally, arecoline disrupts the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), elevates reactive oxygen species (ROS) causing epithelial atrophy, and promotes fibroblast-to-myofibroblast transformation that persists abnormally, all collectively driving progressive collagen accumulation and submucosal fibrosis (Shih et al., 2019; Pant et al., 2015).

A 2025 study on tropomyosin-1 (TPM1) added a further layer to this picture: arecoline-driven TGF-β/Smad3 signalling raises TPM1 expression, and TPM1 in turn blocks a protein called STUB1 that would normally help switch the pathway off, so the fibrotic signal keeps reinforcing rather than fading (Zhu et al., 2025; Yang et al., 2022). This kind of positive feedback loop, once fully mapped, is exactly the sort of target that a defined molecule, rather than a broad antioxidant, would need to interrupt.

3.2 Collagen build-up and impaired clearance

OSF is, at its core, a collagen problem: more collagen is made, and less of it is broken down. TGF-β1 drives expression of collagen genes such as COL1A2, COL3A1, and COL6A1, and raises the activity of procollagen proteinase and lysyl oxidase, which cross link collagen fibres, making them harder to degrade (Shih et al., 2019). At the same time, TGF-β1 increases tissue inhibitor of metalloproteinases (TIMP-1) while lowering active MMP-2 and MMP-9, the enzymes that would normally clear excess collagen (Shih et al., 2019; Shen et al., 2020). Fibroblasts taken from OSF tissue also show a reduced ability to physically engulf and clear collagen through phagocytosis (Shih et al., 2019; Tang et al., 2025). The net effect is a tissue that keeps laying down collagen while steadily losing its capacity to clean it up.

3.3 Myofibroblast transdifferentiation and epithelial-mesenchymal transition

Persistent TGF-β1 signalling pushes ordinary fibroblasts to become myofibroblasts, contractile cells that express alpha-smooth muscle actin (α-SMA) and secrete large amounts of collagen and fibronectin (Shih et al., 2019; Pant et al., 2015). Transcription factors such as Slug, Twist, and ZEB1 drive this shift and, in doing so, silence E-cadherin, a hallmark step of epithelial-mesenchymal transition (EMT) (Shih et al., 2019; Gayathri et al., 2023). EMT is thought to be one of the mechanistic bridges connecting simple fibrosis to the malignant transformation seen in a subset of OSF patients (Chen et al., 2021).

3.4 Autophagy

A somewhat counter-intuitive finding from recent years is that autophagy, usually understood as a protective, house-cleaning process inside cells, appears to help drive OSF forward rather than restrain it. OSF tissue shows raised levels of the autophagy marker LC3, and arecoline-treated fibroblasts that convert into myofibroblasts also show increased LC3-II, suggesting autophagy assists the fibroblast-to-myofibroblast switch rather than opposing it (Li et al., 2016). Arecoline

also damages oral keratinocytes by inducing autophagy and apoptosis, contributing to the epithelial atrophy that is characteristic of OSF (B. Zhu et al., 2020). This matters directly for phytochemical research, because several plant compounds, curcumin included, are known to modulate autophagy (Jalouli et al., 2026; Shakeri et al., 2019). Whether that modulation helps or worsens OSF may depend on dose and cellular context, a question that remains unsettled.

3.5 Long non-coding RNAs (lncRNAs) and microRNAs

In OSF tissue, the lncRNA H19 is overexpressed, and it works by sequestering miR-29b, a microRNA that would otherwise bind and silence COL1A1 messenger RNA. When H19 soaks up miR-29b, collagen production rises. Arecoline itself increases H19 through the TGF-β pathway, so this becomes another loop linking areca nut to collagen accumulation (Yu et al., 2021). Therefore, targeting the H19/miR-29b axis may be an effective approach to relieving the symptoms of OSF. Separately, loss of miR-29c has been shown to promote OSF progression by releasing its restraint on tropomyosin-1 (Yang et al., 2022), while other lncRNAs such as LINC00974 and GAS5-AS1 push TGF-β/Smad signalling in opposite directions, one activating and the other restraining it (Shih et al., 2019). This growing lncRNA/microRNA map is one of the more promising, and still largely unexplored, entry points for phytochemical intervention.

3.6 Oral microbial dysbiosis

Until very recently, almost all OSF research treated the disease purely as a fibroblast and collagen problem. A 2025 study broke from this pattern by asking what areca nut chewing does to the resident oral microbial community. Using a mouse model that combined mechanical irritation, chemical exposure, and areca nut extract to mimic real-world chewing behaviour, the researchers found that areca nut exposure raised both the total abundance and the diversity of oral bacteria, with a marked rise in Streptococcus linked to mucosal injury (Huang et al., 2025). This is among the first serious attempts to connect oral dysbiosis with OSF pathogenesis rather than treating the microbiome as background noise, and it opens a genuinely new question: could phytochemicals with known antimicrobial activity, such as curcumin or tea catechins, act on OSF partly by correcting this dysbiosis, rather than purely through TGF-β1 suppression or antioxidant activity? At the time of writing, no published study has tested this directly, which makes it one of the more concrete openings for a molecular biology-oriented research project.

4. Phytochemicals And Their Molecular Targets

4.1 Curcumin

Curcumin, the yellow polyphenol from turmeric (Curcuma longa), is one of the most extensively studied natural compounds for the treatment of OSF (Al-Maweri, 2019; Shao et al., 2024). Curcumin therapy showed a reduction in the expression of p53, TGF-β, and iNOS in a subset of patients with OSF in one pilot study, however, the changes were not statistically significant compared with pretreatment levels. This does, however, suggest a potential molecular effect (Gupta et al., 2017). Additionally, curcumin exerts anti-fibrotic effects in OSF by modulating cellular autophagy (Shakeri et al., 2019) and by inhibiting the proliferation and migration of activated buccal mucosal fibroblasts (She & Xu, 2024). It has also been shown to suppress fibroblast-to-myofibroblast transitioning in both lung and uterine cells of animal models (Liu et al., 2016; Yang et al., 2026). It also downregulates fibrosis-related proteins, including fibronectin, α-smooth muscle actin (α-SMA), and type I and III collagen, thereby reducing extracellular matrix deposition and fibrosis (She & Xu, 2024). Furthermore, in one study it relieved arecoline-induced

oral submucous fibrosis via inhibiting the LTBP2/NF-κB axis (Zhang et al., 2024), and in another by inhibiting HIF-1α/TGF-β/CTGF signalling pathway (Zhang et al., 2021).

Clinically, a 2024 systematic review and meta-analysis pooling thirteen randomised controlled trials found that curcumin, whether applied topically or taken orally, produced a statistically significant reduction in burning sensation after six months compared with placebo, although it did not significantly outperform active comparators on mouth opening at earlier time points (Shao et al., 2024). Individual trials comparing curcumin against lycopene found roughly equal benefit for mouth opening, burning sensation, tongue protrusion, and cheek flexibility (Piyush et al., 2019; Saran et al., 2018) while trials combining curcumin with intralesional corticosteroid injections reported added benefit over injection alone (Adhikari et al., 2022).

A practical obstacle running through literature is curcumin's poor oral bioavailability: it dissolves poorly in water, degrades quickly, and is cleared rapidly by the liver, so very little reaches the bloodstream after a standard oral dose (Lopresti, 2018). Researchers have tried to work around this through local rather than systemic delivery. A combination tablet-and-mouthwash formulation known as Turmix, which pairs curcumin with piperine to slow its metabolism, improved OSF symptoms on trial (Rai et al., 2019), and buccal mucoadhesive patches loaded with curcumin gel showed benefit by improving mouth opening and reducing burning sensation, while allowing more sustained local release (Chandrashekar et al., 2021). At the nanotechnology level, mucoadhesive zein and beta-cyclodextrin nanoparticles have been engineered specifically to improve curcumin's solubility for buccal delivery (Esposito et al., 2020), although this has not yet been tested directly in OSF patients.

4.2 Lycopene

Lycopene, the red carotenoid pigment found in tomatoes and watermelon, works mainly by scavenging reactive oxygen species and limiting oxidative damage to lipids, proteins, and DNA (Kim et al., 2014). A systematic review analysing 19 clinical studies (N. Gupta et al., 2020) showed that consistent use of lycopene in OSF patients resulted in a statistically significant increase in mouth opening compared to other interventions like spirulina, intralesional injection of steroids & hyaluronidase, aloe vera, methylprednisolone acetate and placebo, and 17 studies found a statistically significant improvement in burning sensation. Because lycopene's proposed mechanism is largely antioxidant (Imran et al., 2020) rather than a direct block on TGF-β1/Smad signalling, it is best understood as complementary to curcumin rather than a substitute working through the same pathway.

4.3 Astaxanthin

Astaxanthin, a carotenoid extracted mainly from microalgae and marketed widely as a nutraceutical, is a more recent addition to the OSF literature. A 2024 randomised, double-blind, placebo-controlled trial gave 68 OSF patients either 5 mg astaxanthin twice daily or a placebo for twelve weeks, and found statistically significant improvement in both mouth opening and burning sensation in the astaxanthin group, with mild and comparable adverse events between groups (Perumal et al., 2024). Another recent study in 2026 conducted in rats (Peng et al., 2026) showed that astaxanthin demonstrated protective effects against arecoline-induced oral submucous fibrosis by improving oral epithelial barrier integrity through upregulation of the tight junction proteins ZO-1 and Occludin. It also inhibited epithelial–mesenchymal transition by increasing E-cadherin and decreasing N-cadherin and Snail expression. Furthermore, astaxanthin preserved mitochondrial homeostasis in oral keratinocytes, suggesting its potential as a therapeutic agent for OSF.

4.4 EGCG

Epigallocatechin-3-gallate (EGCG), the main catechin in green tea, has a more clearly worked-out mechanism than many of its counterparts. Laboratory work has shown that arecoline activates latent TGF-β1 in buccal fibroblasts through mitochondrial reactive oxygen species, and that EGCG suppresses this activation, effectively blocking the conversion of TGF-β1 into its active, fibrosis-driving form at its source (Hsieh et al., 2018). A 2025 review specifically surveying natural anti-fibrotic agents that act on the TGF-β/Smad cascade lists EGCG, curcumin, and several other polyphenols as candidates' worth systematic pharmacological comparison, underlining that the field is actively consolidating around this signalling axis as the primary druggable target (M. Chen et al., 2025).

Beyond these, butylidenephthalide, glabridin, asiatic acid, tanshinones (dihydrotanshinone I, tanshinone I, and tanshinone IIA), and salvianolic acid B appear repeatedly in OSF reviews (Shih et al., 2019). This wider pool of candidates shows that the field is not limited to curcumin, lycopene, and astaxanthin.

5. Relevance To Pakistan And South Asia

Pakistan carries a substantial burden of OSF, driven by use of gutka, paan and naswar. Naswar is one of the most commonly used smokeless tobacco products in Pakistan, particularly in Khyber Pakhtunkhwa (Z. Khan, 2016) and Balochistan, where its use is culturally and socially accepted. It is typically prepared from sun-dried tobacco, slaked lime, ash, and flavouring agents and is placed in the oral vestibule for prolonged periods of time (Irshad et al., 2025). According to the 2014 Global Adult Tobacco Survey (GATS) Pakistan (Naz et al., 2018), 8.6% of the Pakistani population was current users of smokeless tobacco, with greater use in males compared to females. Betel quid use varies substantially by population studied but overall shows a concerning prevalence in Pakistan. A cross-sectional survey of 2140 adolescents from secondary schools of Karachi, Pakistan showed 42.6% were users of betel quid or smokeless tobacco (Hussain et al., 2017). A study in 2020 found Pakistan to have one of the higher overall prevalence rates of betel quid and areca nut practice from selected south Asian countries (Gunjal et al., 2020).

Smokeless tobacco has been linked with development of oral submucous fibrosis, particularly when mixed with betel quid. A molecular study conducted in Pakistan in 2024 (Zaidi et al., 2024), reported that polymorphisms in TP53 exon 4 and p21 (rs1801270) were significantly associated with both OSF and OSCC (oral squamous cell carcinoma), suggesting their involvement in disease pathogenesis.

This is relevant to phytochemical research, as a study (S. Gupta et al., 2017) demonstrated that curcumin can modulate p53 expression in OSF tissue, though findings did not reach statistical significance. That study was conducted in an Indian population; no equivalent investigation has examined whether curcumin or related phytochemicals interact with the specific TP53 and p21 variants identified in Pakistani patients, and therefore remains a relatively unexplored area.

6. Research Gaps For Future Studies

Several gaps stand out clearly from this literature, and each lead to a concrete research question. First, there are clinical trials of curcumin, lycopene, and astaxanthin measure mouth opening and burning sensation, but there is need for trials that pair clinical outcomes with molecular markers such as TGF-β1, CTGF, MMP-2/9, or TIMP-1. Secondly, there is an established link between oral microbial dysbiosis and OSF, however further studies, with phytochemical intervention evaluating the oral microbiome of OSF patients, using 16S rRNA sequencing are required.

Third, the non-coding RNA network around TGF-β signalling, including H19/miR-29b/COL1A1 and miR-29c/tropomyosin-1, is well characterised at the level of arecoline. Given that curcumin is already known to modulate microRNA expression in other fibrotic tissues, checking whether it, or EGCG, or other phytochemicals shifts these specific microRNA levels in OSF-derived fibroblasts is another research direction. Finally, given that Pakistani OSF patients carry distinct TP53 and p21 polymorphisms and are predominantly exposed to naswar rather than the areca nut combinations studied in Indian trials, a locally conducted trial evaluating phytochemical efficacy ideally pairing clinical outcomes with p53 and p21 expression would address a genuine research gap.

7. Conclusion

Oral submucous fibrosis has moved, over roughly the last decade, from being described mainly in clinical terms to being understood as a specific molecular cascade: TGF-β1/Smad activation, collagen cross-linking and impaired clearance, myofibroblast transdifferentiation, autophagy dysregulation, non-coding RNA control, and, most recently, oral microbial dysbiosis. Curcumin, lycopene, and astaxanthin all show real clinical benefit against this backdrop, and mechanistic work has started to explain why, largely through suppression of TGF-β1 signalling and antioxidant activity. What is still missing is work that ties clinical improvement to molecular change, tests phytochemicals against the microbiome and non-coding RNA layers, and is grounded in the genetic and exposure profile of Pakistani patients.

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