



Anti-Fibrotic Effect of Few Herbs and Flavonoids in Treatment of Oral Submucous Fibrosis: A Scoping Review

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ABSTRACT

Background: Chewing tobacco, areca nuts, and their related products can develop oral submucous fibrosis (OSF), a premalignant disease with a high rate of malignant transformation. Due to the increased processing and marketing of areca nut products, which is frequently found in younger age groups, OSF is more prevalent in India and Southeast Asian nations. Clinical signs of OSF, such as constricting bands of collagen in the buccal mucosa, inflammation, and trauma that result in the development of fibroblasts and fibrosis, are used to make the diagnosis and histopathology for confirmation. It has been demonstrated that the main function of herbs and the substances they contain is to stop excessive and aberrant fibrosis in a variety of fibroproliferative disorders.

Methods: A comprehensive search of PubMed, Web of Science, Scopus, Google Scholar, was conducted from 1987 until June 2022. In this review, we observed 8 studies, all were in vitro studies. The primary aim of our systematic review is to concentrate on a thorough assessment of antifibrotic herbs used to treat OSF.

Results: Our studies identified 370 articles of which 8 were selected. All these 8 studies were conducted on cell lines in vitro setup. All these studies show various herbs having anti-fibrotic properties.

Conclusion: All these papers call for more research on these anti-fibrotic compounds and point to a possible method for finding novel anti-fibrotic medications by screening more plant materials.

Keywords – Oral submucous fibrosis (OSF); potentially malignant disorders; Areca nut, Antifibrotic

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INTRODUCTION

The most prevalent cancer of the oral cavity is oral squamous cell carcinoma (OSCC), which accounts for 90% of all oral cancers. [1] Numerous factors, including alcohol, cigarettes, areca nuts, genetic susceptibility, and hormonal considerations, are thought to be risk factors.[2] It is widely known that the development of cancer in the oral mucosa occurs in two stages, starting with the presence of a precursor lesion and progressing to cancer. Thus, specific alterations in the oral mucosa typically precede the majority of OSCC. Potentially malignant diseases are the term used to describe these warning lesions (PMD). One of the most typical PMDs detected in the oral mucosa is oral submucous fibrosis (OSF). [3]

According to recent research, areca nuts high copper concentration may be just as significant to OSF pathogenesis as the nut's alkaloids.^{4,5}The OSMF has a long history and is well-known. OSF was identified as a mouth and throat disorder and given the name Vidhari by Sushruta, a great Indian physician who lived in the period between 2500 and 3000 BC.^{6,7}

Oral submucous fibrosis (OSF) can affect any area of the mouth cavity including, in rare cases, the throat. Even though vesical formation may occasionally be preceded by or associated with it, it is always linked to a juxta-epithelial inflammatory response, followed by fibroelastic changes of the lamina propria and epithelial atrophy, which causes the oral mucosa to stiffen, resulting in trismus and the inability to eat.⁸

The practise is common among South Asian cultures, but it is now also acknowledged in North America and Europe. The frequency of OSF has significantly increased as a result of the areca nut and tobacco combo.⁹ OSF initially manifests as inflammation. The oral mucosa blanches and takes on a marble-like appearance following inflammation, indicating hypovascularity and fibrosis. Blanching may be localised, reticular, or widespread. Small vesicles that rupture and create erosions can sometimes form.^{9, 11} A fibrous ring that limits mouth opening (trismus) is typical of the later advanced stage of OSF.^{10, 11}

Fibroblast proliferation and extracellular collagen matrix formation are the two different steps that are involved in OSF.^{12, 13}the importance of fibroblasts as a key cell type in tissue repair and wound healing is well known. Myofibroblast are a special kind of cells that are phenotypically intermediate between fibroblast and smooth muscle cells. Myofibroblast have been linked to conditions where extracellular matrix (ECM) deposition is enhanced and fibrosis develops as a result.¹⁴

For years, managing of OSF has been difficult for oral doctors. Several herbal preparations are readily available in the current therapeutic environment and claim to be helpful in the treatment of OSF. Herbal medicine offers an intriguing array of potential modulators of this process; these therapies may prevent fibrosis or cure it if it already exists in a healthy way. In certain more extreme circumstances, they may even be able to destroy pathologic cirrhotic tissue.¹⁵Throughout human history, medicinal herbs have been used in a variety of ways, including as treatment methods, in many regions of the world.¹⁶

1) REVIEW METHODOLOGY

Search technique Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria were used for the literature search (PRISMA). From 1987 to June 2022, comprehensive automated literature searches were done on PubMed (English), Medline, Scopus database, Google Scholar. When the first pool of articles was checked for references, more papers emerged that had been overlooked by automated searches. Search keywords used were only 'OSMF or OSF and antifibrotic herbs (n=20)', only 'Malignant transformation of OSMF (n = 9)', 'Management of OSMF (n = 8)' and 'antifibrotic herbs in OSF (n = 18)'. In Fig.1, a PRISMA flowchart for the current review is displayed.

2.1) Research question

The research question was framed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines, as well as the Participants, Interventions, Control, and Outcomes principle.¹⁷

We framed the question as: "Among OSF patients (P), what is the effectiveness of Antifibrotic (I) herbs as compared to standard steroid treatment (C) in the management of OSF (O)?"

2.2) Inclusion criteria –

- (1) Articles published in English language only.
- (2) In vitro and In-vivo studies which included only OSF & treatment of OSF with Antifibrotic herbs.

2.3) Exclusion criteria-

- (1) Studies that are redundant, repetitious, and unrelated.
- (2) Research on conditions other than OSF that are premalignant of the mouth.
- (3) Conference papers and case studies.
- (4) Non-English language articles.

2.4) Data extraction

Two reviewers meticulously analyzed all qualifying articles independently and extracted pertinent information, including author names, publication years, and conclusions. Disagreement between the reviewers was resolved through discussion, until final consent.

For the purpose of qualitative analysis, observational studies & in vitro studies – were included.

2) RESULT:

Study Selection

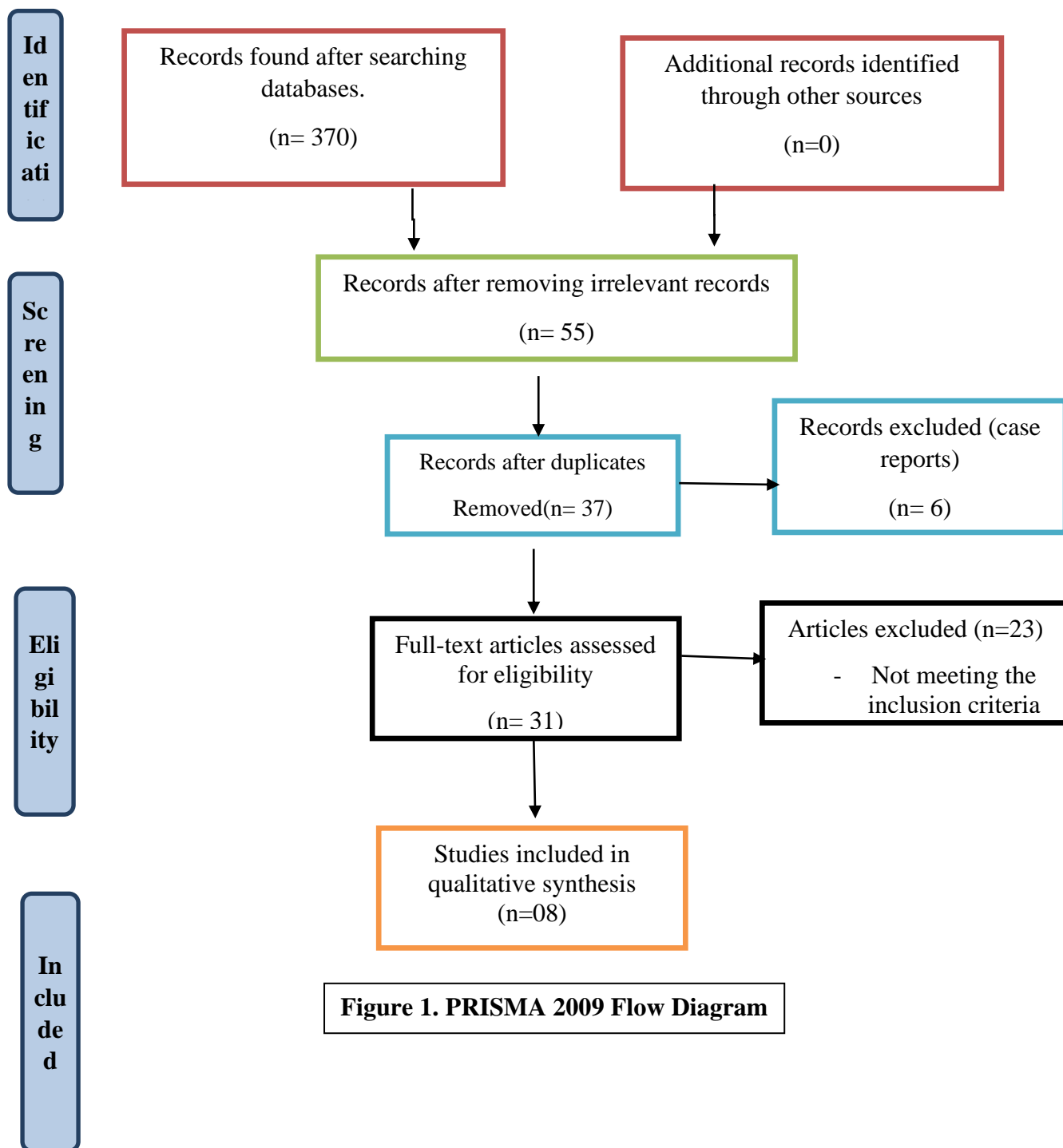


Fig. 1 - Flowchart of the Preferred Reporting Items for Systematic Reviews for selection of articles.

The search strategy resulted in the retrieval of 55 articles from the databases. In addition, 70 results were obtained from Google Scholar which were screened for relevance and three articles were selected for closed review. A total of 31 articles were obtained after removing duplicates full-text screening.

3) DISCUSSION

The most common cause of OSF and a major global source of morbidity and mortality is fibrosis, which is defined by extracellular matrix (ECM) build-up and disruption of normal tissue architecture.¹⁸

TABLE 1: ANTIFIBROTIC EFFECTS OF SELECTED HERBAL EXTRACTS

Herbs/models	Constituents/ Extracts	Results	Type of study	Citation
In –vitro model for fibrosis	Buccal Fibroblast Cell Culture	Developed a vitro model of primary buccal fibroblast for in vitro experiments of fibrosis.	In Vitro	Pooja et al 2019
In –vitro model fibroblast for arecoline effect	Fibroblasts Cultured In Vitro From Normal Buccal Tissue	Concluded that OSF fibroblast shows slightly higher basal rate of collagen synthesis than normal fibroblast	In Vitro	Meghji et al 1969
Scutellaria baicalensis	Baicalin	Exhibits Antifibrotic in vitro by inhibiting the TGF-B1 pathway	In Vitro	Hu et al. 2009
Tulsi	Ocimum Sanctum Linn	Downregulating expression of TGF-B1, COL1A2, COL2A1.	In Vitro	Adtani et al. 2018
Tinospora cordifolia	Thunb.	Antifibrotic activity by significant reduction of CTGF, COL1A1.	In Vitro	Shankargoud a Patil et al 2021
Turmeric	Curcuma Longa	Obstructs proliferation of myofibroblasts, interrupts the cell cycle, prompts apoptosis and decreases the generation of collagen type I and III in myofibroblasts.	In Vitro	Shan et al. 2012
Licorice	Glycyrrhizin	SMA, Col1-1, and TGF-1 expression were all downregulated.	In Vitro	Amritha et al. 2022
Centella asiatica	Asiatic acid, Madecassic	Attenuated arecoline-induced TGFb1, COL1A2, and	In Vitro	Adtani P et al Eric Y et al.

	acid,	COL3A1 expression levels a		2017
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The traditional Indian system of health care and longevity is known as Ayurveda. Ayurvedic medicine treats the patient as an organic whole and involves the healthful use of medications, foods, and certain practises. There have been several proposed therapy modalities for OSF, but none have been demonstrated to be curative, therefore the quest for an appropriate treatment modality is currently ongoing. Since the beginning of time, plants have been a significant source of medicine. Studies from all over the world have been done to demonstrate the benefits of herbs for OSF.¹⁶

In a study by Hu et al., flavonoids and nonflavonoids found in 21 Chinese herbs were evaluated for their antifibrotic activity in vitro. Using TGF 1, fibrosis was produced in rat kidney fibroblasts. Utilizing calorimetric techniques, the total collagen buildup was evaluated. They had furthermore carried out immunofluorescence labelling for the expression of collagen 1 and alpha smooth muscle actin, as well as reverse transcription polymerase chain reaction (RT PCR) analysis for COL1A2 mRNA. According to their research, five substances—quercetin, baicalein, baicalin, salvianolic acid B, and emodin—showed potential to reduce the amount of total collagen accumulated as measured by spectrophotometry and to suppress collagen 1 and alpha smooth muscle actin at both the protein and mRNA levels.¹⁸

In India, the use of herbal remedies containing natural ingredients and medicinal plant extracts has been used for a very long time as a reliable, inexpensive, and non-invasive technique of treating a variety of illnesses.¹⁹ this article's goal is to review assessment of various herbal remedies that have been utilised to treat OSF.

4.1) Curcumin

Turmeric contains the naturally occurring yellow pigment curcumin, which has a broad range of biological effects.^{16,20} The most significant active polyphenolic component responsible for the biological action of turmeric is called curcumin (1,7-bis(hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione).^{16,21}

Curcumin, the main component of turmeric (*Curcuma longa*), which makes up 2-5% of the herb, is a medicinal plant with a variety of therapeutic effects, including anti-inflammatory, antioxidant, and anticancer characteristics, a fibrinolytic effect.²²

Numerous researchers from throughout the world have investigated the pharmacological effects of curcumin. Curcumin has the potential to lessen both recent and ongoing inflammation. It decreases inflammation by reducing histamine levels and maybe increasing the adrenal glands' synthesis of endogenous cortisone.⁶ In the OSF affected tissues, myofibroblasts, which are normally thought of as activated fibroblasts, can be seen. Analysis reveals that curcumin suppresses the proliferation of fibroblasts and myofibroblasts show curcumins potential antifibrotic effect.²³

A study was carried out by Agarwal N et al. to evaluate the effectiveness of turmeric in 30 OSF patients. The burning feeling and mouth opening both improved. It was proposed that curcumin inhibits a variety of molecules involved in inflammation, hence exerting its anti-inflammatory effects. Due to their capacity to suppress lipid peroxidation and restrain cellular

proliferation, they also possess fibrinolytic properties, which slow down the pace of collagen formation.^{16, 24}

Deepa DA et al. were studied efficiency of curcumin and turmeric delivered in two distinct forms, namely curcumin capsules and turmeric oil, was examined in 48 individuals with OSF. Clinical indications and symptoms of individuals receiving curcumin and turmeric oil treatment showed statistically significant improvement. It had fibrinolytic and anti-inflammatory effects.^{16, 25}

Curcumin is a promising drug in the management of OSF, according to several research. Due to its pharmacological properties, curcumin administration over an extended period of time significantly improved OSF patient outcomes.

Turmeric was found to be effective as fibrinolytic in treatment of OSF in all 7 studies. All the studies included in this review have reported improvement in OSF patients.

4.2) Nigella sativa

The medicinal herb *Nigella sativa* (Family Ranunculaceae) is employed in several conventional medical practises, including Unani, Ayurveda, and Siddha. It is indigenous to Southern Europe, North Africa, and Southwest Asia and is frequently referred to as black seed.

Numerous studies have shown that the pharmacological effects of *Nigella sativa* cover a wide range, some of which may include immunomodulatory, anticancer, anti-inflammatory, and antioxidant capabilities.²⁶ Thymoquinone, a bioactive component of *nigella sativa*, is thought to be responsible for the majority of these medicinal effects.²⁶

According to Papalia PR et al investigation of the efficacy of turmeric combined with black pepper and *nigella sativa* on 40 OSF patients, the mouth opening, burning sensation, and superoxide dismutase levels were all improved.^{22, 27}

Nigella sativa was found to be effective as fibrinolytic in treatment of OSF in all 3 studies. All the studies included in this review have reported improvement in OSF patients.

4.3) Licorice

One such herb that is utilised in conventional medicine is licorice. According to available data, transforming growth factor (TGF), a key mediator of fibrosis, is directly harmed by licorice's active component, glycyrrhizin. Additionally, the aglycone of glycyrrhizin, glycyrrhetic acid, a crucial mediator in the TGF-mediated fibrosis pathway.¹⁹ To assess its anti-fibrotic activity in the oral cavity, the phytochemical of choice in the current investigation was licorice. Due to its powerful anti-inflammatory and anti-microbial characteristics, licorice has been used for generations in traditional medicine to treat a wide range of ailments, including sore throats, ulcers, and other conditions. Glycyrrhizin and isoflavonoids including Glabrene, Isoliquiritigenin, and glabridin are only a few of the active components found in licorice.¹⁹ Licorice was found to be effective as fibrinolytic in treatment of OSF in two studies.

4.4) Centella asiatica/ Gotu kola

Centella asiatica, sometimes known as "gotu kola," is a plant that was once native to South and Southeast Asia but is now found throughout the tropics. For people with fibrotic diseases, gotu kola is a very safe medication that is highly advised.¹⁵ Numerous clinical studies have shown that gotu kola is a highly effective vulnerary. It also appears that this herb prevents abnormal scar formation by promoting healthy wound healing.¹⁵

4.5) Baicalin

Scutellaria baicalensis extract, a plant that is known as baicalin, exhibits antifibrotic activities in a number of fibrotic conditions.^[15] In a research by Hu et al., the antifibrotic efficacy of flavonoids and nonflavonoids identified in 21 Chinese herbs was assessed in vitro. Their investigation revealed that baicalin has antifibrotic potential by inhibiting collagen 1 and alpha-smooth muscle actin at the protein and mRNA levels and lowering total collagen accumulation as assessed by spectrophotometry.¹⁸

4.6) Tulsi

By blocking the enzymes that cause inflammation, tulsi (basil or *Ocimum sanctum* Linn) improves metabolism, immunity, and inflammation levels. Additionally, recognised for lowering stress levels and having antioxidant properties, tulsi.²²

In a different recent work by Adtani et al., the antifibrotic activity of buccal fibroblasts was examined in vitro using extracts of *Ocimum basilicum* (Tulasi) and linalool. The study discovered that these herbal extracts have antifibrotic effect because they drastically reduced the expression of the TGF- and collagen genes.¹³

4.7) *Tinospora cordifolia* (Thunb.) Miers

It is commonly known as 'Guduchi' or 'Giloy', is discovered to grow in India's mountainous regions. The plant belongs to the Menispermaceae family and has flowers that range in colour from yellow to green. The Indian Pharmacopoeia contains information on this plant's therapeutic properties. It is known that medicinal plant extracts include a variety of phytochemicals with potential to have anti-inflammatory, immunomodulatory, and antioxidant effects that may have an Antifibrotic effect.²⁸

4) Antifibrotic Activity of Herbal Extracts

Pooja et al carried out after collecting healthy oral tissue, the primary cell culture process was carried out. In order to rule out chromosomal abnormalities, karyotyping was done. Extracellular matrix (ECM) was qualitatively demonstrated by immunofluorescence labelling and Masson trichrome staining using a panel of fibroblast-specific markers (vimentin, phalloidin, transforming growth factor- receptor 1 [TGF-R1] and s100a4) (MTS). On the ninth day after seeding, a monolayer of oral fibroblasts was identified, they observed. The patient sample analysis revealed no chromosomal abnormalities. Vimentin, phalloidin, TGF-R1, and s100a4 positive staining was seen, confirming the cell type. Fibroblasts with spindle shape and sparse ECM were discovered using MTS. They came to the conclusion that the study established a procedure for developing and describing a basic buccal fibroblast cell culture model.²⁹

According to a study by Meghji et al., neither the rate of fibroblast proliferation in culture nor the rate at which they hydrolyzed the betel nut alkaloid arecoline to arecaidine significantly differed between fibroblasts cultured in vitro from normal buccal tissue and tissue from oral submucous fibrosis (OSF) associated with betel nut chewing. Although the OSF cells had slightly greater basal rates of collagen synthesis, these rates were increased to the same level upon arecoline addition in both normal and OSF cells.³⁰

Adtani et al. used extracts of *Centella asiatica* Linn and its bioactive component Asiatic acid to assess the antifibrotic activity in buccal fibroblasts generated with arecoline in vitro. They came to the conclusion that both extracts were successful at reducing the expression of the collagen genes COL1A2 and COL3A1, as well as fibroblastic markers like TGF- β and fibroblastic markers like TGF- β .³¹

5) LIMITATIONS

This systematic review has some limitations. Databases of Ayurvedic and Unani literature weren't examined because they weren't searchable using popular search engines. In our investigation, we included publications that could only be found in English literature. Additionally, none of the studies are from Southeast Asia, where OSF is extremely common; they are all from India. It's possible that some studies from those nations were published in local journals rather than the databases consulted here, which would result in publication bias.

6) CONCLUSION

Even while prevention is the best medicine, treating OSF with natural remedies is better for patients in the long run after the disease has already set in. Alternatives to intrusive methods for the therapeutic care of OSF's early phases include medications with an herbal origin that practitioners can use. Many antifibrotic herbs have a great deal of potential for treating a variety of illnesses marked by excessive fibrosis in patients. There is a significant function for herbal medicine that has just recently been fully understood or accepted. In addition to treating symptoms, herbal treatment also gets rid of the underlying causes of illness. In conclusion, this analysis convincingly shows how herbal products can prevent oxidative stress, inflammation, and fibrogenesis while also protecting the oral mucosa. Antifibrotic herbs are potentially a viable treatment option for the care of patients with OSF, according to the evidence compiled from this systematic review on their usage in OSF.

Acknowledgements Conflicts of interest

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