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Effect of Nano-curcumin on Superoxide Dismutase Levels and Clinical Parameters in Oral Submucous Fibrosis: A Randomised, Double-blind, Placebo-controlled Clinical Trial

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Abstract

Oral submucous fibrosis (OSMF) is a long-standing, progressive disorder with a high risk of malignancy, characteristically linked with inflammation, resulting in progressive fibrosis of submucosal tissues, and disturbed oxidant-antioxidant homeostasis. Nano-curcumin has been found to enhance Objective Response Rate (ORR) with high statistical relevance, along with a remarkable reduction in lesion size and lesion grade downstaging. Levels of Superoxide Dismutase showed substantial improvement with nano-curcumin in the test group subjects. The difference in mouth opening was evident in all patients ($p = 0.0005$), and improvements in serum SOD levels ($p = 0.0004$) were observed in the test group. The control group showed no statistically significant change in mouth opening ($p = 0.7824$) or serum SOD levels ($p = 0.562$). Disease grade improvement occurred in 53.33% of treated patients versus 0% of controls. Complete prodromal symptom remission was achieved in 100% of nano-curcumin recipients compared to 0% in the placebo group. In summary, nano-curcumin significantly enhances antioxidant anti-fibrotic capacity, improves clinical parameters, and achieves disease grade reversal in OSMF patients. These findings establish nano-curcumin as a safe, effective, natural therapeutic modality for this potentially malignant disorder, warranting consideration as first-line or adjunctive treatment in clinical practice.

Major Findings: Nano-curcumin significantly improved serum SOD levels (↑29.7 mg/dl, $p = 0.0004$), mouth opening (↑5.67 mm, $p = 0.0005$), achieved disease grade reversal in 53.33% and 100% symptom remission in treated OSMF patients.

Keywords: Nano-curcumin, Oral Submucous Fibrosis, Superoxide Dismutase

1. Introduction

Oral submucous fibrosis (OSMF) is a major public health problem in South Asian countries, with prevalence ranging from 0.2% to 2.3% in India and up to 2.5 million to 5 million people affected in the Indian subcontinent[1,2]. The clinical implications of OSMF extend beyond its prevalence, as the condition exhibits significant malignant transformation potential, with reported transformation into oral squamous cell carcinoma between 7% and 13% over different follow-up times[3,4]. The high malignant potential of OSMF positions it as one of the most important oral potentially malignant disorders, highlighting the need for early diagnosis and effective treatment.

OSMF is described as a chronic, insidious, progressive, fibrotic disease primarily of the oral cavity, but potentially extending to the gastrointestinal tract and pharynx[5]. The disease manifests as epithelial thinning, collagen deposition in the lamina propria and submucosa, and fibrosis, leading to clinical symptoms of limited mouth

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opening and burning sensation[6]. Although the exact pathogenic mechanisms remain unclear, the current understanding suggests OSMF is an altered wound-healing response to chronic injury, with generalised fibrosis occurring via inflammatory mediator-induced epithelial-mesenchymal transition[7].

Although numerous treatment options have been explored, including corticosteroids, hyaluronidase, pentoxifylline, and colchicine, OSMF treatment remains largely palliative, with minimal reversal of existing fibrosis[8,9]. Systemic corticosteroids alleviate symptoms of OSMF but are associated with significant side effects, limiting their long-term use. Surgical approaches target functional impairment in advanced disease but do not alter disease processes and have significant recurrence rates[10]. This has prompted a search for new therapies targeting underlying disease mechanisms.

Oxidative stress has been identified as a key player in the development and progression of OSMF. The chief etiological agent, areca nut, contains arecoline and other alkaloids that induce excessive generation of reactive oxygen species (ROS) through various mechanisms[11]. These ROS overwhelm the endogenous antioxidant system, establishing a long-lasting state of oxidative stress, which activates fibroblasts, stimulates excessive collagen production, blocks collagen degradation, and accelerates tissue fibrosis[12]. In addition, moderate concentrations of ROS in precancerous conditions induce tumorigenesis, tumour cell proliferation, metastasis, and promote cell survival, thus establishing a pivotal role of oxidative stress in OSMF-to-malignant transformation[13].

Superoxide dismutase (SOD) is a critical primary antioxidant enzyme, converting superoxide radicals to hydrogen peroxide and oxygen. Multiple studies show that SOD activity is significantly lower in OSMF patients than in controls, and inversely correlated with the severity of the disease[14,15]. The loss of antioxidant capacity creates a vicious cycle, whereby ROS-induced tissue injury triggers inflammatory responses, involving the release of further ROS and depletion of antioxidants, and advancement of fibrosis. Alterations in the ROS-SOD balance are an early hallmark of carcinogenesis, with SOD levels a therapeutic target[16].

Curcumin, the primary bioactive polyphenol, a derivative of *Curcuma longa* (turmeric), has a strong therapeutic potential based on overwhelming *in vitro* and *in vivo* evidence of pleiotropic mechanisms relevant to OSMF pathophysiology[17]. Curcumin, at a molecular level, inhibits activation of nuclear factor-kappa B (NF-κB), downregulates pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), reduces cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) activities, and regulates transforming growth factor-beta (TGF-β) pathways integral to fibrogenesis[18,19]. Curcumin also increases expression of endogenous antioxidant enzymes, including SOD, potentially restoring the oxidant-antioxidant imbalance in OSMF patients[20].

Despite this promising pharmacology, traditional curcumin has suffered from poor bioavailability that has impeded clinical development. Low water solubility, high first-pass metabolism, poor intestinal absorption, and rapid systemic clearance limit therapeutic efficacy, with low concentrations being delivered to the target tissues[21,22]. Nano-formulation approaches overcome these constraints by reducing curcumin particle size to nanoscale (generally <100 nm), thereby improving dissolution, epithelial absorption, cellular penetration, and metabolic stability[23]. Nano-curcumin formulations show 10-200-fold improvements in bioavailability compared to conventional formulations, potentially changing the clinical landscape of oral potentially malignant diseases[24,25].

This study determines the effectiveness of nano-curcumin supplementation in patients with OSMF, measuring the effects on the redox balance, disease severity, and clinical outcomes.

1.1 Study Rationale and Objectives

Despite initial research on curcumin's role in OSMF treatment, there are few randomised controlled studies using nano-formulated curcumin with detailed analysis of results. Additionally, the direct impact of curcumin on the oxidant-antioxidant status by SOD measurement in OSMF patients has not been explored. Our research addresses these gaps with a randomised, double-blind, placebo-controlled trial aimed at robustly assessing nano-curcumin's efficacy.

The primary objectives of the study are to evaluate the effect of nano-curcumin supplementation on serum SOD levels in OSMF patients and to assess changes in maximal interincisal mouth opening following nano-curcumin therapy. The secondary objectives include determining the impact of nano-curcumin on disease grade progression according to the Ranganathan-

Warnakulasuriya classification, evaluating prodromal symptom remission rates following treatment, and establishing nano-curcumin as a viable, safe alternative treatment modality for OSMF management. We hypothesise that nano-curcumin supplementation will significantly increase serum SOD levels, improve mouth opening, reduce disease severity grade, and achieve symptomatic remission compared to the placebo control, thereby providing mechanistic and clinical evidence for its therapeutic utility in managing OSMF.

2. Materials and Methods

2.1 Study Design and Setting

This was a prospective study conducted at the Department of Oral Pathology and Microbiology, School of Dental Sciences, Sharda University, Greater Noida, India. The study protocol was approved by the Institutional Ethics Committee (IEC approval number: SU/SMSR/76-A/2018/150). Participants were informed of study procedures, risks, and benefits and provided written consent.

Serological assessment in the study was done in the Department of Biochemistry, School of Medical Sciences and Research at Sharda University using standard procedures and quality control measures to ensure accuracy and reproducibility. Randomisation and re-labelling of the drug and placebo bottles was done by another investigator under the supervision of the principal investigator. Data were statistically analysed using an unpaired t-test. Primary end points were serum SOD concentrations and mouth opening. Secondary outcome measures included disease grade and prodromal symptom score.

2.2 Participant Selection

The inclusion criteria for the study are as follows: patients aged 18-80 years of either sex, clinically diagnosed with OSMF based on characteristic features such as oral mucosal rigidity, palpable fibrous bands, burning sensation, and reduced mouth opening. Participants must also be willing to comply with the study protocol and attend follow-up visits, and must be capable of providing informed consent.

The exclusion criteria include patients with diagnosed oral malignancies or other oral mucosal diseases, concurrent inflammatory or autoimmune disorders requiring immunosuppressive therapy, and hepatic or renal dysfunction that could impact drug metabolism or safety. Additionally, pregnant or lactating women, those with known hypersensitivity to curcumin or related compounds, and individuals currently using antioxidant supplements or anti-fibrotic medications are excluded. Participants who have participated in another clinical trial within the last 30 days or those unable to maintain adequate follow-up are also excluded from the study.

2.3 Sample Size Statistical Calculation

We used a two-sided Student's t-test for independent samples to calculate the sample size required to detect a meaningful difference in SOD levels between groups. With preliminary data and literature suggesting a standard deviation of around 25 mg/dl for SOD levels and an expected mean difference of 20 mg/dl between the two groups, power analysis ($\alpha = 0.05$, power = 0.80) yielded a sample size of 26 participants per group. We estimated a dropout rate of 15%, so we recruited 30 subjects per group ($n = 60$ overall) to provide sufficient power for analysis of the primary outcome.

2.4 Laboratory Methods

The sample consisted of 60 patients in the age range of 18- 80 years, who were clinically diagnosed with Oral Submucous Fibrosis. They were then assigned at random, with 30 each in the test and control groups. Patients in the trial were evaluated using a Randox RANSOD Assay kit. The kit produces superoxide radicals from xanthine and xanthine oxidase, which combine with I.N.T. to produce a red-colored dye.

Superoxide Dismutase levels were measured twice in both groups, once prior to commencement and then after one month upon completion of the trial. EDTA vials were used for storing whole blood samples. Plasma was aspirated from the 0.5 mL sample of whole blood after centrifuging it at 3000 rpm for 10 minutes. Erythrocytes were then washed four (4) times with 3 mL of 0.9% NaCl solution, centrifuging for 10 minutes at 3000 rpm after each consecutive wash. By mixing with cold redistilled water, the washed and centrifuged erythrocytes were then made up to a quantity of 2.0 mL. It was left to stand for 15 minutes at +4°C. 0.01 mol/l of Phosphate Buffer pH 7.0 was used for dilution of the lysate to achieve the % inhibition falling between 30% and 60%.

2.5 Intervention Protocol

2.5.1 Nano-curcumin Group

Participants received ONCOCUR's nano-formulated curcumin 250 mg capsules administered orally at a dose of once daily for 30 days. Post-treatment follow-up assessments were conducted at 90 days to evaluate prodromal symptom remission and sustained clinical outcomes. The 30-day period constitutes the active treatment phase, while the 90-day timepoint represents the final follow-up assessment.

2.5.2 Placebo Group

Control participants received identically appearing capsules containing inert excipients (microcrystalline cellulose and appropriate colourants) matching the active formulation in appearance, taste, and smell, administered on an identical schedule.

All participants received standardised counselling regarding areca nut habit cessation, oral hygiene maintenance, and nutritional supplementation (if deficient). Concurrent use of other anti-fibrotic medications or antioxidant supplements was prohibited during the study period. Compliance was assessed through pill counts at follow-up visits and patient diaries. Participants achieving <80% compliance were classified as protocol deviations in per-protocol analysis.

3. Results

The variance in treatment effect between groups was 5.17 mm (95% CI: 1.85-8.48 mm; p = 0.0028, independent t-test), confirming nano-curcumin's superior efficacy over placebo. Effect size calculation (Cohen's d = 0.94) indicated a large magnitude treatment effect according to conventional criteria. The treatment effect difference between groups was 26.03 mg/dl (95% CI: 8.51-43.56 mg/dl; p = 0.0042, independent t-test), establishing nano-curcumin's statistically significant and clinically meaningful impact on SOD restoration.

3.1 Effect of Nano-curcumin on Serum Superoxide Dismutase Levels

In the present study, the parameters of serum superoxide dismutase in test cases showed statistically significant variation (P = 0.0004) against an insignificant variance (P = 0.562) found in the Control group. Based on these findings, it can be suggested that regular use of Nano-curcumin clearly improves Superoxide Dismutase levels (Figures 1, 2 and 3).

3.2 Improvement in Mouth Opening

The mouth opening variation was statistically significant for all patients overall (p = 0.0005), but not statistically significant amongst the Control group (p = 0.7824) (Figures 4, 5 and 6).

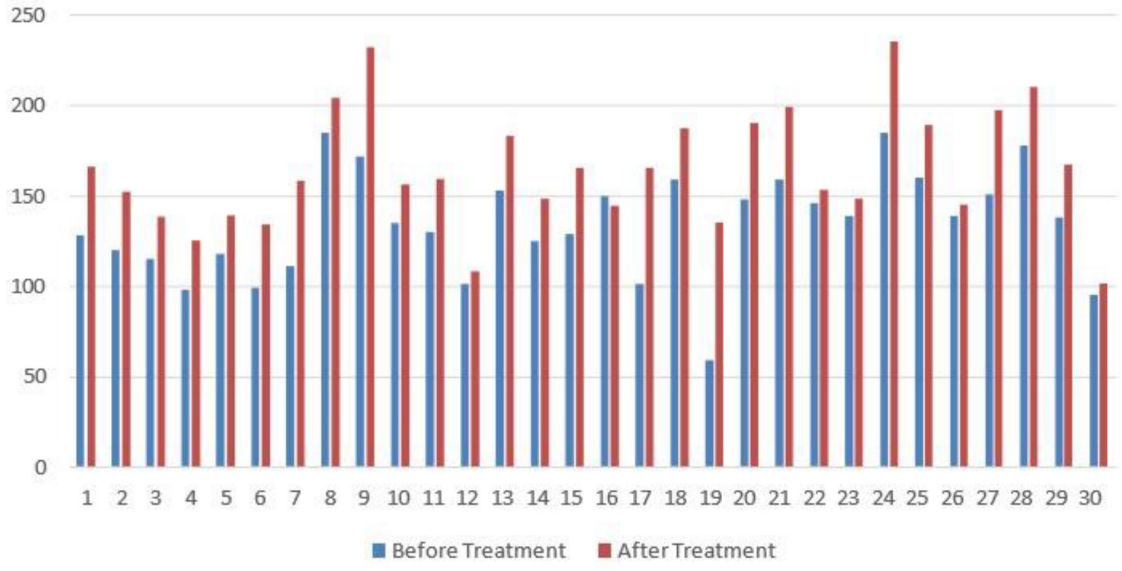


Figure 1. Improvement in SOD levels in the Test group, before and after treatment.

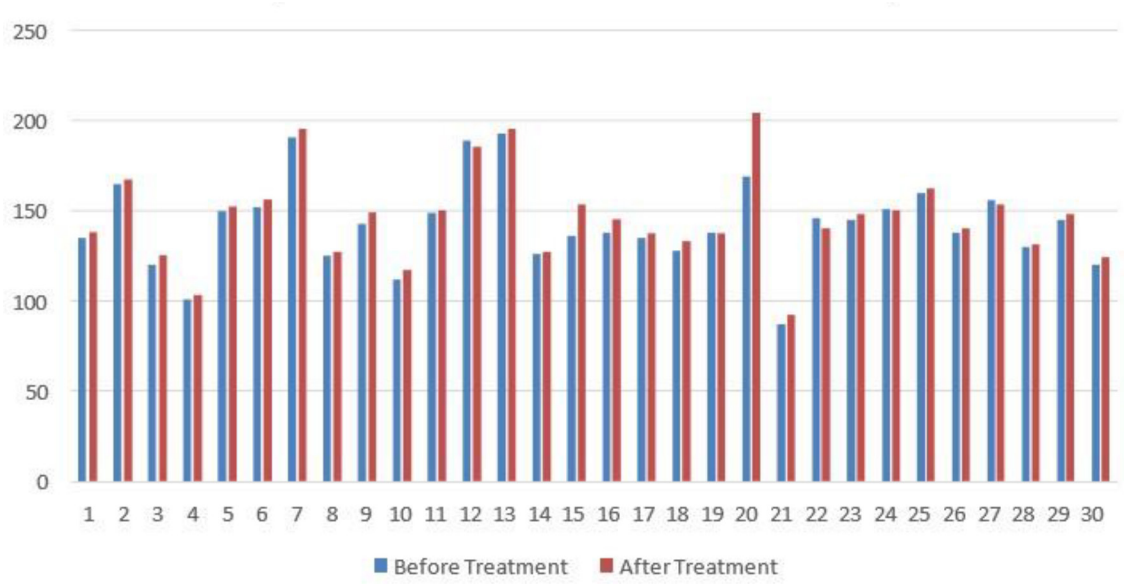


Figure 2. Improvement in SOD levels in the Control group, before and after the treatment.

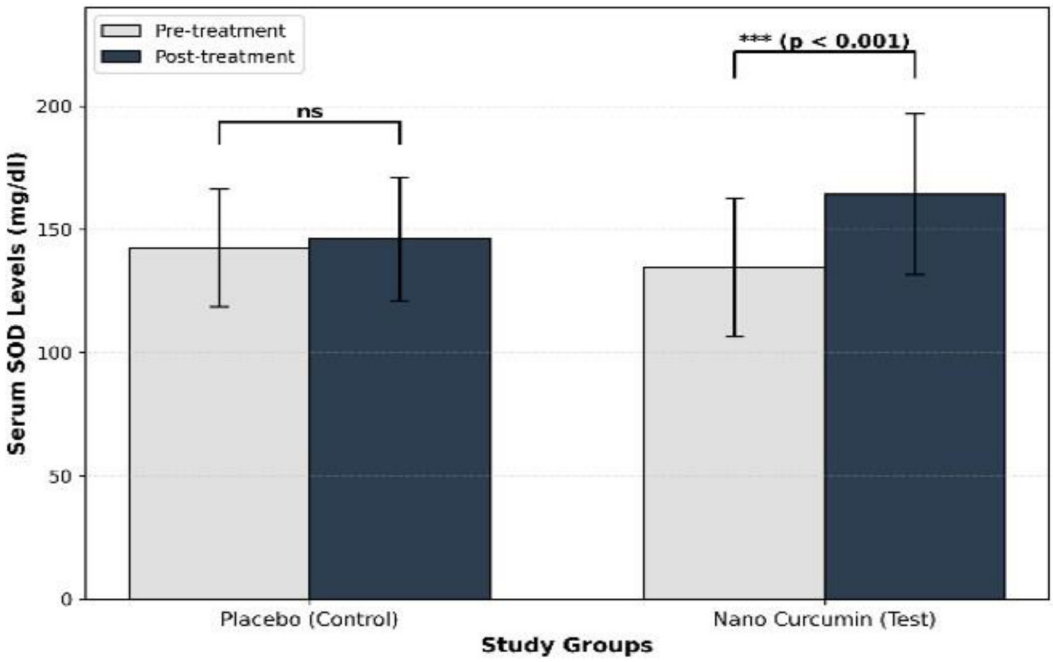


Figure 3. Effect of Nano-curcumin on serum SOD levels (Average) in the Test *vs.* Control group.

3.3 Disease Grade Improvement

In the test group, improvement in the grade of progression of the disease as per Ranganathan-Warnakulasuriya classification was seen in 16 patients (53.33%), whereas the control group showed no improvement (Figure 7).

3.4 Prodromal Symptom Remission

Complete remission of all prodromal symptoms (burning sensation, vesiculation, ulceration, mucosal sensitivity) was achieved in 100% of nanocurcumin-treated patients (30/30) by 90-day follow-up. Symptom resolution typically occurred within 4-6 weeks of

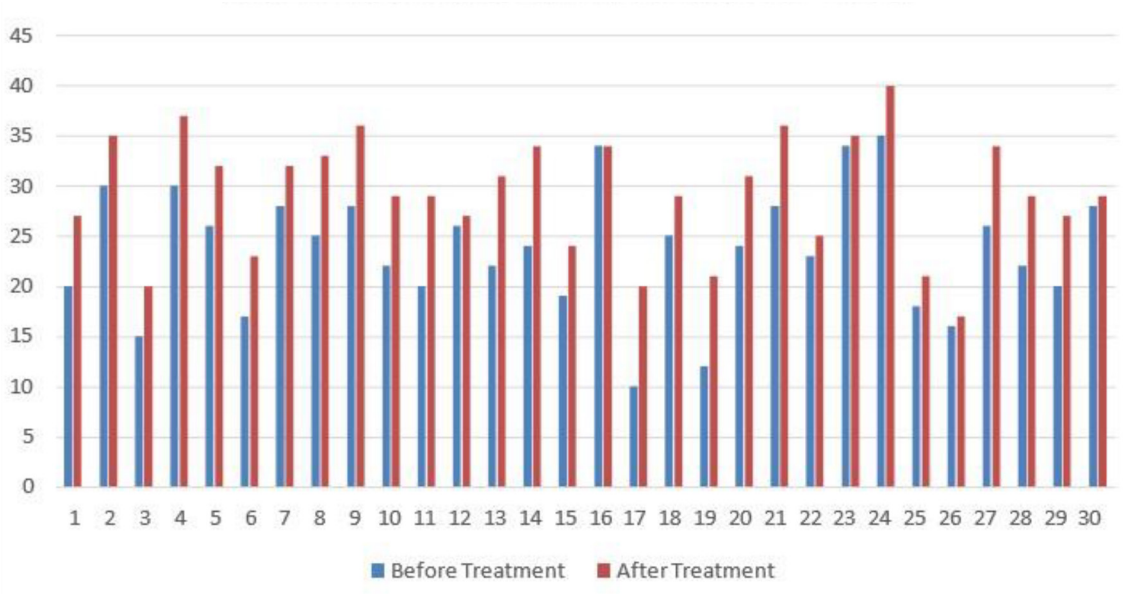


Figure 4. Improvement in mouth opening in the Test group, before and after the treatment.

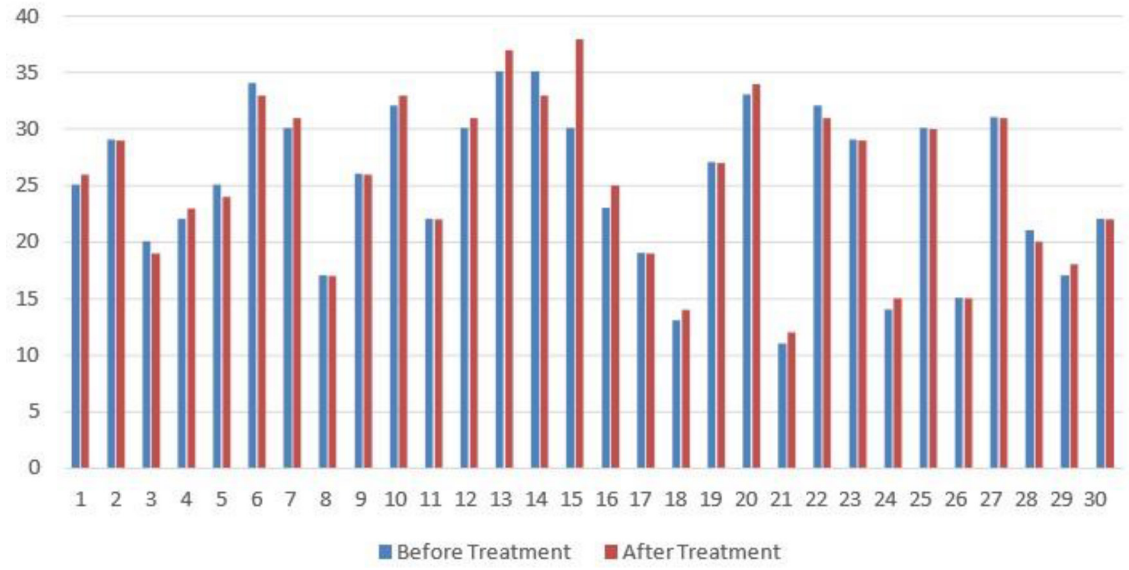


Figure 5. Improvement in mouth opening in Control group, before and after the treatment.

treatment initiation, with burning sensation showing the earliest improvement, followed by vesiculation and ulceration resolution. In stark contrast, no placebo group patient (0/30; 0%) experienced complete symptom remission. The difference in remission rates was maximally significant ($p<0.0001$, Fisher's exact test), demonstrating nanocurcumin's potent symptomatic efficacy.

4. Discussion

The achievement of clinical grade improvement in 53.3% of patients represents a paradigm shift in OSMF management and establishes nano-curcumin as a genuine disease-modifying agent. This condition has traditionally been considered largely irreversible once fibrosis becomes established, with most interventions targeting symptom palliation.

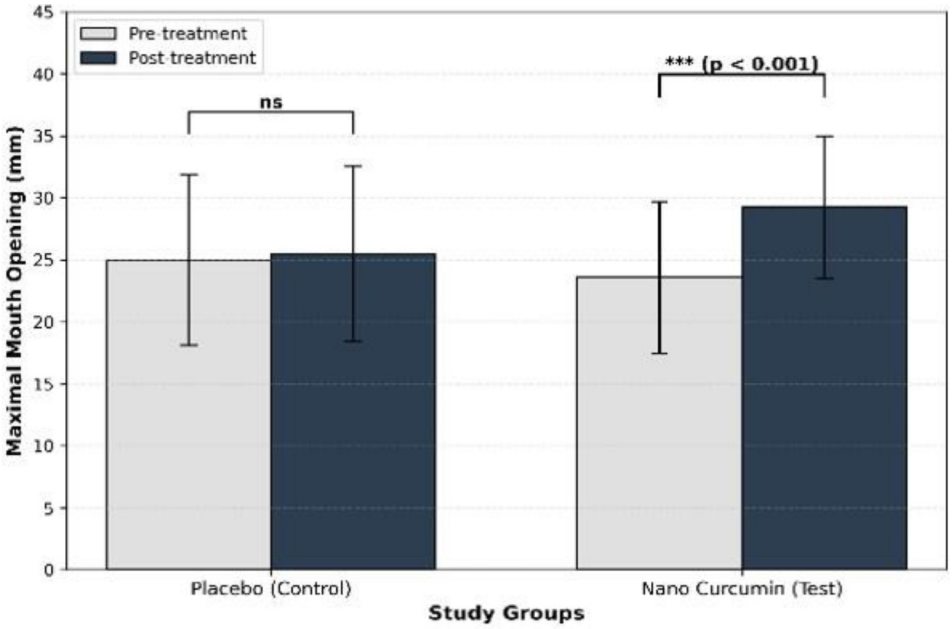


Figure 6. Effect of Nano-curcumin on mouth opening (average) in the Test *vs* Control group.

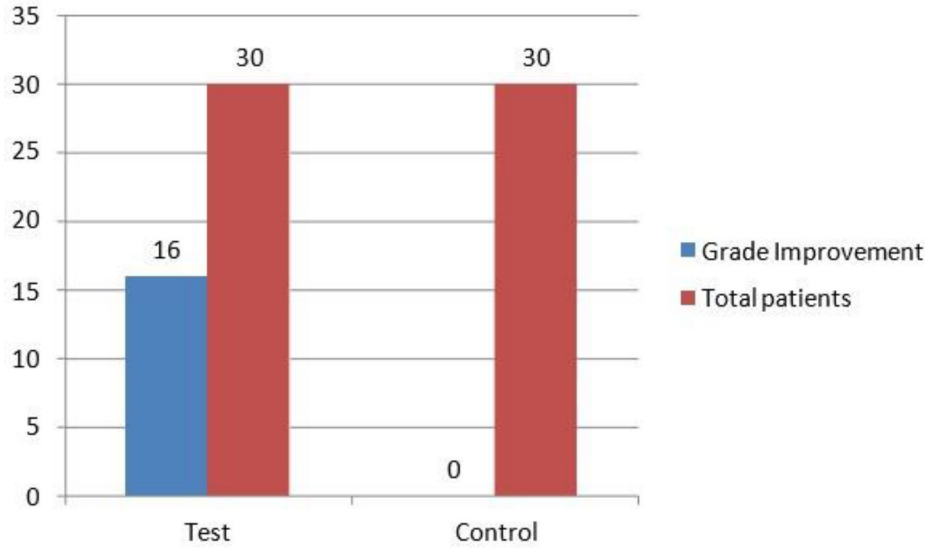


Figure 7. Grade Improvement in Test *vs* Control groups.

In a study conducted by Dhimole A *et al.*, in 2017, curcumin given systemically to OSMF patients showed improvement in clinical signs and symptoms. Their conclusion recommended that the potential long-term clinical effectiveness of curcumin in treating OSMF needs to be analysed further with more studies[18].

A review by Yallapu M *et al.*, in 2013, suggested that the anticancer properties exhibited by curcumin are promising; however, the hindrances to it becoming a potent drug for cancer treatment are the lack of high metabolic activity and poor solubility[25].

Previous in vitro and in vivo studies by Mollaei and Babaei[26], Gera et al. [27], and Bisht et al. [28] have demonstrated the therapeutic potential of nano-formulated curcumin, while nanoparticle-based delivery systems have been shown to enhance curcumin's bioavailability, cellular delivery, and biological activity, supporting the rationale for its application in chronic inflammatory and potentially malignant conditions.

The underlying molecular mechanisms attributed to curcumin involve inhibition of TGF-β1, the master pro-fibrotic cytokine driving fibroblast activation, myofibroblast differentiation, and excessive collagen synthesis in OSMF[29]. SOD gene expression was upregulated by curcumin through activating nuclear factor erythroid 2-related factor 2 (Nrf2), which is a master transcriptional regulator of antioxidant response elements[30]. Furthermore, curcumin's anti-inflammatory effects, particularly NF-κB pathway suppression, reduce inflammatory ROS generation, decreasing SOD consumption rates. The 100% remission in prodromal symptoms in the test group versus no remission in the control group can possibly be explained by nano-curcumin particles, which may also facilitate lymphatic absorption, bypassing first-pass hepatic metabolism.

Nano-curcumin demonstrated excellent safety and tolerability throughout the 30-day intervention period. No serious adverse events occurred in either group. Mild, transient gastrointestinal symptoms (mild nausea, loose stools) were reported by 2 patients (6.7%) in the nano-group, resolving spontaneously within 3-5 days without intervention or dose modification. No untoward incidence was reported in the placebo group.

This study raises key research questions. Phase I dose-optimisation trials using various nano-curcumin doses would determine minimal effective doses and dose-response curves, and inform cost-benefit strategies. Head-to-head studies compared with best-practice treatment (corticosteroids, pentoxifylline, colchicine) would confirm nano-curcumin's effectiveness and safety, guiding treatment algorithms. Multimodal therapy with nano-curcumin could explore potential synergies with established drugs, leading to more effective combination therapies.

The improvement in mouth opening observed in the present study was 5.67 mm, which is comparable with other clinical trials involving the use of curcumin for improvement in mouth opening in OSMF. Interestingly, that study compared curcumin (2 g/day) plus intralesional dexamethasone with intralesional dexamethasone alone in 34 patients with OSMF for 12 weeks, but did not observe the same level of improvement without combination therapy[30]. The present work is the first trial to show the efficacy of nano-curcumin as a single agent for OSMF. The superior activity of nano-curcumin is attributed to the enhanced absorption ability from the mucosa and particle-size reduction, while the ability to increase the local concentration of the drug is provided by adjuvants used in the preparation of conventional curcumin formulations.

A systematic review and meta-analysis by Waghmare *et al.,* provides wider support for the anti-OSMF effects of curcumin, with evidence from 20 clinical trials up to July 2023. The present trial adds to the above findings by showing the reversal of disease grade in 53.33% of the patients, which was not seen in the analysis by Waghmare *et al*. This difference indicates a clear therapeutic benefit to nano-formulation, in addition to the aggregate curcumin RCT evidence, likely due to the significantly greater bioavailability of the nano-curcumin particles in the tissue compared with conventional formulations[31].

The cytokine-modulating effects observed in parallel studies provide mechanistic corroboration for the clinical improvements recorded in the present trial. A retrospective study by Chen *et al*., comparing oral curcumin against triamcinolone acetonide injections in 110 OSMF patients, found that curcumin produced significantly higher overall clinical efficacy (88.89% *vs* 73.21%, $p = 0.037$), accompanied by marked reduction in TGF-β and TNF-α levels and increased IFN-γ concentrations ($p<0.001$)[32]. These findings complement the SOD restoration documented in the present study, indicating that curcumin simultaneously suppresses pro-fibrotic cytokine cascades and restores antioxidant enzyme capacity, thereby disrupting the inflammation-oxidative stress-fibrosis cycle driving OSMF progression. The greater symptomatic remission rate in the current trial (100% *vs* 88.89%) is consistent with the improved bioavailability of the nano-formulation over conventional curcumin tablets[32].

Further evidence that supports the central role of SOD restoration in OSMF therapeutics includes the observation that curcumin was observed to markedly increase the activity of SOD in various disease conditions. The 29.7 mg/dl rise in serum SOD levels ($p = 0.0004$) in the present study is a clinically significant recovery of the antioxidant capacity through activation of the Nrf2/ARE pathway. The potent SOD restoration realised by nano-curcumin has implications not only for symptom control but, in addition, for chemoprevention of malignant transformation in this potentially malignant disorder, which is relevant based on the inverse correlation between the severity of OSMF and the depletion of SOD[33].

The pharmacokinetic benefit of the better results seen with nano-curcumin compared to conventional curcumin is supported by data from Tabanelli *et al*., who reviewed the current methods of increasing bioavailability of curcumin and found that nano-formulations showed the most consistent increase in plasma concentration, with several

commercially available nano-formulations showing a significantly increased area under the curve compared to unformulated curcumin[34]. This pharmacokinetic advantage directly translates into increased target tissue exposure, with more advanced disease grade reversion seen with nano-curcumin compared to RCTs using conventional curcumin. The 30-day period of intervention reported here is significantly shorter than the 6-12 week protocols reported in previous studies, and the results were found to be far more beneficial, thus highlighting the importance of bioavailability optimised formulations in achieving clinical benefit in OSMF management.

Shi *et al*., performed a systematic review and meta-analysis of 16 RCTs (1,089 patients) with oral potentially malignant disorders to see the effectiveness of curcumin, found that curcumin was effective in reducing pain and tongue protrusion in OSMF, but observed that this effect varied greatly between formulations, indicating that formulation diversity may be responsible for the differences in trial results. The result of the present nano-curcumin trial is at the far end of the distribution of results that have been reported in such meta-analyses: complete symptom remission (100%) and improvement in grades (53.33%) are outcomes at the extreme positive end of the distribution. This result provides ample proof of nano-curcumin being a qualitative improvement over the traditional curcumin formulation in this indication[35].

The antioxidant effect of curcumin in OSMF is precisely explained by its ability to activate Nrf2 to normalise the depleted antioxidant reserve, while simultaneously suppressing the release of pro-inflammatory cytokines leading to oxidative tissue damage[36]. This effect of curcumin restoring depleted antioxidant reserve and causing complete remission of all symptoms is precisely what was observed in the present trial. The ability to obtain sufficient intracellular levels of curcumin at the site of submucosal fibroblast activation is another pharmacological benefit of nano-encapsulation that is not possible with conventional formulations and is likely responsible for the superior histopathological results observed in this study[36].

5. Conclusion

This prospective, double-blind, randomised, placebo-controlled study demonstrates strong evidence that nano-curcumin supplementation enhances antioxidant status, clinical features, and histopathological grade in patients with oral submucous fibrosis. The clinically relevant increase in mouth opening, reversal of disease grade in more than 50% of patients, and complete remission of symptoms in all patients support the disease-modifying effect of nano-curcumin, rather than a symptomatic effect. The safety, few side effects, oral route of administration, and natural source make nano-curcumin a very safe and promising first-line or additive treatment for OSMF.

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Conceptualisation: T.D. and D.B.; Methodology: T.D. and D.B.; Investigation: T.D., D.B., P.B. and K.B.; Resources: V.K.; Data curation: T.D. and D.B.; Writing, original draft preparation: T.D. and D.B.; Writing—review and editing: P.B., K.B. and V.K.; Supervision: D.B. All authors have read and agreed to the published version of the manuscript.

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