International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018

Risk of Liver Fibrosis Assessment in Areca Nut Induced Potentially Malignant Disorders: A Case Control Study

Dr. Jampani Ramadevi[1], Dr. M.Chandra Sekhar Reddy[2], Dr.Sajjala Srinivasa Reddy[3]

[1]post Graduate Student, Department of Oral Medicine and Radiology, [2] Professor& Head of the Department, Department of Oral Medicine and Radiology, [3] Post Graduate Student, Department of Oral Medicine and Radiology

Date of Submission: 20-11-2025 Date of Acceptance: 30-11-2025

ABSTRACT

Background: The International Agency for Research on Cancer (IARC) updated its judgment in 2004 that areca nut alone and betel quid with or without tobacco were harmful to humans. Chemical hepatocarcinogenesis may be accelerated by areca nut. Oral sub mucous fibrosis (OSF), other oral potentially malignant disorders (OPMDs), and malignant disorders (MDs) have all been linked to areca nut components, according to research.

Objectives: In this study, the relationship between betel nut chewing and the development of oral sub mucous fibrosis and other potentially malignant disorders was examined, along with an assessment of the risk of liver fibrosis.

Methodology: It is a type of case-control study for duration of one year. Based on the chosen groups and exclusion criteria, a total of 120 subjects were chosen. Following the completion of a thorough case history, blood samples were obtained in order to perform liver function testing (Serum Glutamic Oxaloacetic Transaminase (SGOT),Serum Glutamic Pyruvic Transaminase (SGPT). Following the gathering of lab reports, the outcomes were evaluated, examined, and connected to each subject's case history.

Results: The descriptive statistics show that SGOT and SGPT values remain identical between controls and other PMDs due to Betel Nut Habit, with a mild numerical rise in OSMF patients. However, the increased SD in OSMF indicates greater variability and reduces statistical significance.

Conclusion: The present study showed the increased SGOT, SGPT levels in OSMF, compared to patients with other PMD's and control group. When compared to patients with other PMDs caused by betel nut, OSMF patients are at increased risk of developing liver fibrosis even though statistically not significant.

Keywords: Oral submucous fibrosis, potentially malignant disorders, Liver fibrosis, Betel nut

I. INTRODUCTION

Consumption or chewing of areca nut (AN), the seed (endosperm) found in the fruit of the Areca catechu tree, is a cultural habit in the tropical countries of South Asia, the Asian Pacific region, and some parts of East Africa(1) AN causes oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) such as oral submucous fibrosis (OSF), oral leukoplakia (OL), oral erythroplakia (OE) and lichenoid reactions(2)(3). In addition, AN-induced OPMDs have recorded various rates of malignant transformation(4).

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent liver illnesses nowadays. It has been linked to obesity, hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease, and even death. (5) Furthermore, NAFLD raises the risk of liver fibrosis, cirrhosis, and hepatocellular cancer (6). Hepatocellular carcinoma is one of the most frequent, dangerous, and common malignant human tumors. Chewing betel nut which contain nitrosamines, may cause methylation and cyanoethylation of liver DNA, causing hepatocytegenotoxicity and, in the long run, liver cancer. Chemically, areca nuts may cause hepatocarcinogenesis. The betel leaf, on the other hand, has significant quantities (15 m-1g fresh weight) of safrole, which is known to induce liver cancer in rats(7)

People of Asian heritage are more likely to have oral sub mucous fibrosis (OSMF), a potentially cancerous condition (8). It is a long-term inflammatory disease marked by increasing oral connective tissue fibrosis that restricts mouth opening and makes eating, swallowing, and speaking more challenging. It has been shown to be an oral precancerous illness with a 7.6% malignant transformation rate. (9)

There is strong evidence from a number of studies that areca nut is the main etiological cause of OSF. The role of areca nut components in the pathophysiology of OSF has been extensively

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018

studied over the past 20 years. The majority of the clinical features seen in elucidating the genesis and pathophysiology of this illness are evidently explained by fibrosis and hyalinization of sub epithelial tissues (8).

Chewing of betel nuts has a significant risk of oral cancer oral cancer development(8). There is a dose-response link between the amount of quid consumed daily and the length of chewing time and the risk of oral cancer. (9)

Therefore, this study aids in the early detection of liver toxicity in patients with OSF and other potentially malignant disorders, it may also demonstrate that OSF and liver toxicity can co-occur with betel nut as an independent risk factor; and it may aid in the determination of the incidence of risk of liver toxicity in the patients with betel nut chewing habit with potentially malignant disorders other than oral sub mucous fibrosis. And also this study aimed at estimation of haemoglobin levels in patients with betel nut chewing habit.

II. MATERIALS AND METHODS

A total of 120 participants from the Rayalaseema region (Kadapa district) were divided into 3 groups 40 individuals in each group according to the inclusion and exclusion criteria listed below. Group 1 consists of patients who chew betel nuts and have a history of OSF; Group 2 consists of patients who chew betel nuts but have no history of other PMDs (such as leukoplakia, lichenoid contact response, or erythroplakia); and Group 3 consists of patients who do not chew betel nuts and have no history of OPMDs (control group). The study groups' inclusion criteria included those who chewed areca nuts and healthy, normal individuals in the control group. Additionally, patients ranging in age from 18 to 45 were included.

Criteria for exclusion Patients on medications that cause liver toxicity, patients with any other co-morbid condition, patients who should not regularly smoke or drink alcohol, patients with a history of hepatitis B virus (HBV) infection, patients with a history of hepatocellular cancer, patients with a history of alcohol consumption, patients with any systemic disease that may cause live fibrosis, older people over 45 because they would be susceptible to physiologic fibrotic changes in the liver.

A total of 120 subjects—40 from each group—were chosen from the Oral Medicine and Radiology outpatient clinic. Before the trial started, each participant gave their informed consent, institutional ethical committee approval was done. To gather data on age, sex, educational attainment, and betel nut eating habits, a structured questionnaire was created.

It was deemed usual to chew one or more arecanuts daily for a minimum of one year. With the aid of a questionnaire, each patient provides a thorough case history with regard to liver function. Following the collection of each subject's case history, blood samples were taken under appropriate aseptic circumstances without causing any harm to the subjects. The obtained samples were sent to the lab for a liver function test. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) levels were measured, examined, and correlated with each subject's case history following the gathering of lab reports.

III. RESULTS

Data was entered in MS Excel and imported to SPSS version 26. A total of three groups were compared: healthy controls (Group 3), individuals with other PMDs due to betel nut chewing habit (Group 2), and clinically diagnosed OSMF patients (Group 1). Welch's one-way ANOVA was used to assess differences in biochemical parameters across the groups. The analysis revealed no statistically significant differences in SGOT ($p = 0.444$) or SGPT ($p = 0.892$) levels among the three groups. However, a numerical increase in mean values was observed in the OSMF group compared to the other two groups. Descriptive statistics revealed that both SGOT and SGPT levels were comparable in controls and individuals with other OPMDs due to betel nut, with a mild increase in OSMF; however, the large variability within the OSMF group reduced statistical significance. Overall, the findings highlight that although liver enzyme levels show a non-significant upward trend with the progression from habit to disease.

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018

TABLE 1. Welch One-Way ANOVA for SGOT, SGPT and Haemoglobin

Variable	F-value	df1	df2	p-value
SGOT	0.825	2	48.4	0.444
SGPT	0.115	2	45.6	0.892

P<0.05* is considered statistically significant

The Welch ANOVA results indicate that SGOT (p = 0.444) and SGPT (p = 0.892) do not differ significantly among the three groups—controls, betel nut chewers, and OSMF patients. Although enzyme levels tend to rise slightly in OSMF, the differences are not statistically meaningful.

TABLE 2. Descriptive Statistics of Biochemical Parameters across Groups

Variable	Group	N	Mean	SD	SE
SGOT	**Control**	39	30.15	8.71	1.40
	other PMDs due to Betel Nut Habit	39	30.15	8.71	1.40
	OSMF	21	33.81	12.14	2.65
SGPT	**Control**	39	35.26	8.51	1.36
	other PMDs due to Betel Nut Habit	39	35.26	8.51	1.36
	OSMF	21	37.05	16.41	3.58

P<0.05* is considered statistically significant

The descriptive statistics show that SGOT and SGPT values remain identical between controls and other PMDs due to Betel Nut Habit, with a mild numerical rise in OSMF patients. However, the increased SD in OSMF indicates greater variability and reduces statistical significance.

TABLE 3A. Games–Howell Post-Hoc Test for SGOT

Comparison	Mean Difference	p-value
Control vs other PMDs due to Betel Nut Habit	**0.00**	**1.000**
Control vs OSMF	**–3.66**	**0.450**
other PMDs due to Betel Nut Habit vs OSMF	**–3.66**	**0.450**

P<0.05* is considered statistically significant

Post-hoc comparisons reveal no difference in SGOT levels between controls and other PMDs due to betel nut (p = 1.000). Although OSMF patients exhibit higher SGOT (mean difference ~3.66 U/L), the difference remains statistically non-significant (p = 0.450). This suggests only a non-significant upward trend in SGOT with disease progression.

TABLE 3 B. Games–Howell Post-Hoc Test for SGPT

Comparison	Mean Difference	p-value
Control vs other PMDs due to Betel Nut Habit	0.00	1.000
Control vs OSMF	–1.79	0.887
Other PMDs due to Betel Nut Habitvs OSMF	–1.79	0.887

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018

P<0.05* is considered statistically significant

SGPT levels are identical between controls and other PMDs due to betel nut, and although slightly higher in OSMF patients, the difference is not significant (p = 0.887). SGPT does not appear to be a reliable biochemical indicator distinguishing early exposure (habit alone) from established OSMF.

Table 4: Descriptives

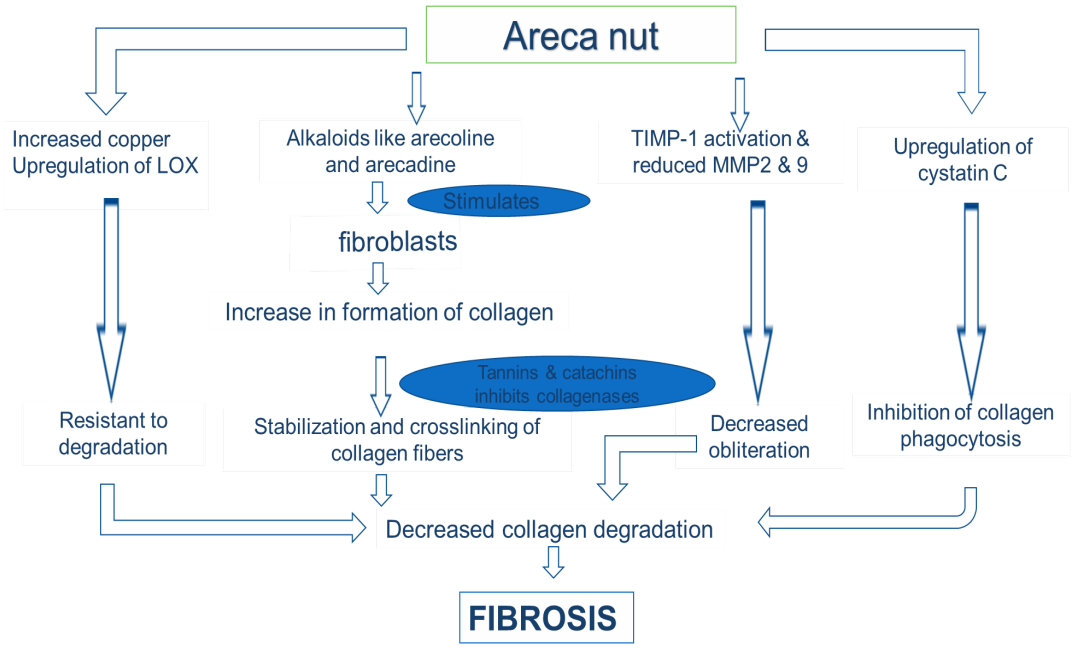
Group	N	Mean Age (years)	SD (years)
OSMF	21	38.48	3.66
other PMDs due to Betel Nut Habit	39	35.90	5.13
Control	39	36.26	5.19

IV.

V. DISCUSSION

The majority of chronic liver illnesses involve structural and functional changes, including liver fibrosis.(10)OSMF is primarily observed in areca nut users which are severe, progressive, and morbid illness.(11) The aberrant fibroblast deposition in the underlying connective tissue is the cause of the marked rigidity of the oral mucosa, which eventually reduces the mouth's opening.(12) Chewing areca nuts can cause burning sensations and sporadic oral mucosal ulcers on the lips and soft palate. Chewing areca nuts is strongly linked to the development of OSMF, leukoplakia, and oral cancer. (13)(14)Due to common dietary or cultural practices, the disease is unique in that it is limited to a certain geographic area. The majority of Indians chew areca nuts together with tobacco. There was a direct correlation between OSMF and chewing frequency. (15) Extensive experimental research has demonstrated that areca nut is carcinogenic and mutagenic. (16,17) The areca nut's arecoline and arecadine are primarily in charge of aberrant fibroblast development and collagen synthesis, which cause OSMF's connective tissue to gradually change. (18)(19)(20)(21). Collagen is cross-linked by lysyl oxidase, while areca nut flavonoids, chatechin, and tanin further stabilize the process. (22)(23)(flowchart 1)

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018



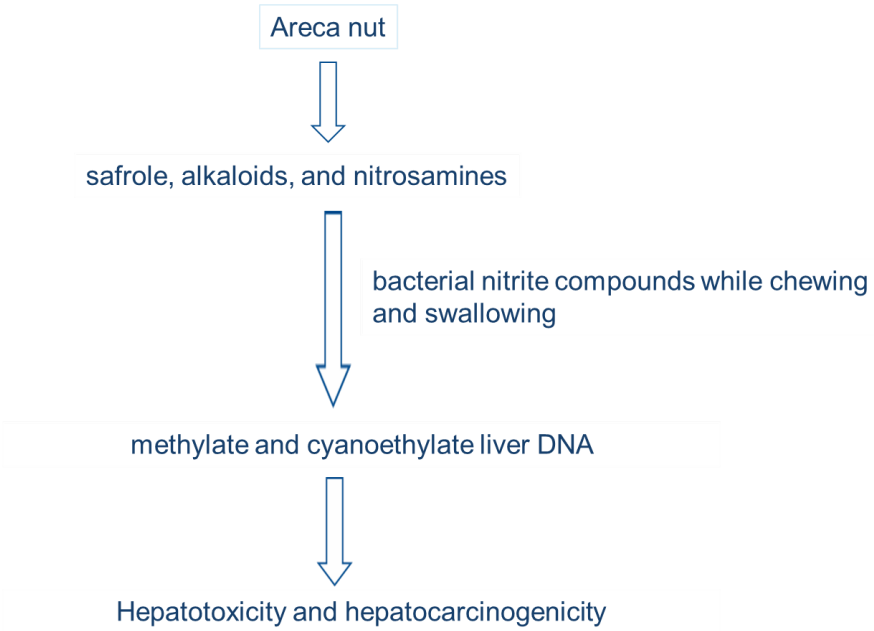
FLOW CHART 1: MECHANISM OF FIBROSIS BY ARECANUT

According to the current study, it is a younger age group disease that primarily affects men rather than women, which is consistent with earlier research. (24)(25)(26) All areca nut chewing participants with OSMF, other PMDs either by itself or in conjunction with tobacco, lime, or piper betel leaf.

The majority of the study participants were regular kharrha users. Mature white half-cut areca nut pieces are combined with tobacco and lime in the manual preparation known as kharrha. Gutkhawas taken by majority of patients in group 2. Chewing areca nuts in any form took an average of five to seven years. The average amount consumed in any form each day was between 24 and 28 g, and the average frequency of consumption was two to six times each day. According to Shah and Sharma, daily consumption was more important than the habit's overall duration.(27) According to Ahmed et al., people who have been using areca nuts continuously for longer than five years are more likely to develop OSMF.(28)

When compared with healthy controls, other PMDs and OSMF had higher mean serum SGOT and SGPT, and a positive link was discovered. Transaminase levels in OSMF patients were shown to be significantly elevated by CD Anuradha and C. S. Shyamala Devi.(29)Choube and Bhowate found that OSMF and OSMF with oral lichenoid lesion had higher levels of transaminase, alkaline phosphatase bilirubin, and HCV RNA. (30)Studies carried out in Thailand have shown that a large increase in liver enzymes in areca nut users is associated with a high risk of developing liver cirrhosis and liver cancer. (31)The high concentration of safrole, alkaloids, and nitrosamines in areca nut and its metabolites, as well as their interaction with bacterial nitrite molecules during chewing and swallowing, are responsible for their hepatotoxicity andhepatocarcinogenicity. (32) (flow chart 2)

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018



FLOW CHART 2: MECHANISM OF HEPATOTOXICITY BY ARECA NUT

Nitrosamines unique to areca nuts have the potential to methylate and cyanoethylate liver DNA, which is harmful to hepatocytes. (32) Additionally, liver fibrosis, scleroderma, and other fibrotic disorders have been linked to lysyl oxidase. (33) Extensive collagen deposition akin to OSMF results from unnecessary suppression of matrix metalloproteinase enzymes, and safrole and arecoline work in concert to boost MMP-9 (TIMP-1) production. (34) In addition to causing oral cavity fibrosis, elevated TIMP-1 in the blood may also be responsible for the fibrotic alterations in the liver.

VI. CONCLUSION

The present study showed the increased SGOT, SGPT levels in OSMF, compared to patients with other PMD's and control group. This indicates that Areca nut specific nitrosamines may methylate and cyanoethylate liver DNA which is genotoxic to hepatocytes.When compared to patients with other PMDs caused by betel nut, OSMF patients are at increased risk of developing liver fibrosis even though statistically not significant. Clinician treating the cases of OSMFshould consider liver functioning tests before formulating treatment plan.

REFERENCES

[1]. Senevirathna K, Pradeep R, Jayasinghe YA, Jayawickrama SM, Illeperuma R, Warnakulasuriya S, et al. Carcinogenic Effects of Areca Nut and Its Metabolites: A Review of the Experimental Evidence. Clin Pract. 2023 Feb 21;13(2):326–46.

[2]. Betel-quid and Areca-nut Chewing and Some Areca-nut-derived Nitrosamines - NCBI Bookshelf [Internet]. [cited 2025 Nov 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK316567/

[3]. Global epidemiology of areca nut usage - Gupta - 2002 - Addiction Biology - Wiley Online Library [Internet]. [cited 2025 Nov 12]. Available from: https://onlinelibrary.wiley.com/doi/10.1080/13556210020091437

[4]. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis - Chen - 2008 - Cancer Science - Wiley Online Library [Internet]. [cited 2025 Nov 12]. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1349-7006.2008.00863.x

[5]. Chou YT, Li CH, Sun ZJ, Shen WC, Yang YC, Lu FH, et al. A Positive Relationship between Betel Nut Chewing and Significant Liver Fibrosis in NAFLD Subjects, but Not in Non-NAFLD Ones. Nutrients [Internet]. 2021 Mar 11 [cited 2025 Nov 12];13(3). Available from: https://www.mdpi.com/2072-6643/13/3/914

[6]. Mittal SS, Mohod S, Lohe V, Patel S, Khubchandani M, Kukde MM. Role of Betel Nut in Liver Toxicity in Oral Submucous Fibrosis and Oral Cancer Patients: A Case-Control Study. Cureus. 2023 Nov;15(11):e48562.
[7]. Tsai JF, Chuang LY, Jeng JE, Ho MS, Hsieh MY, Lin ZY, et al. Betel quid chewing as a risk factor for hepatocellular carcinoma: a case-control study. Br J Cancer. 2001 Mar;84(5):709–13.
[8]. Su SY, Chen WT, Chiang CJ, Yang YW, Lee WC. Oral cancer incidence rates from 1997 to 2016 among men in Taiwan: Association between birth cohort trends and betel nut consumption. Oral Oncol. 2020 Aug 1;107:104798.
[9]. Areca Nut and Oral Cancer: Evidence from Studies Conducted in Humans - S. Warnakulasuriya, T.H.H. Chen, 2022 [Internet]. [cited 2025 Nov 12]. Available from: https://journals.sagepub.com/doi/10.1177/00220345221092751
[10]. Dangore-Khasbage S, Bhowate R. Assessment of Risk of Liver Fibrosis in Areca Nut Habitual by Ultrasound Elastography. J Datta Meghe Inst Med Sci Univ. 2019 Dec;14(4):315.
[11]. Gupta PC, Ray CS. Epidemiology of betel quid usage. Ann Acad Med Singapore. 2004 July;33(4 Suppl):31–6.
[12]. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966 Dec;22(6):764–79.
[13]. Jeng JH, Chang MC, Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. Oral Oncol. 2001 Sept;37(6):477–92.
[14]. Bhowate RR, Lohe VK, Meshram MG, Dangore SB. Serum aflatoxin B1 antibody titer, percent hemolysis and transaminases in oral submucous fibrosis. J Oral Maxillofac Pathol JOMFP. 2021;25(1):110–7.
[15]. Bhowate RR, Lohe VK, Meshram MG, Dangore SB. Serum aflatoxin B1 antibody titer, percent hemolysis and transaminases in oral submucous fibrosis. J Oral Maxillofac Pathol JOMFP. 2021;25(1):110–7.
[16]. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum. 2004;85:1–334.
[17]. Prokopczyk B, Rivenson A, Bertinato P, Brunnemann KD, Hoffmann D. 3-(Methylnitrosamino)propionitrile: occurrence in saliva of betel quid chewers, carcinogenicity, and DNA methylation in F344 rats. Cancer Res. 1987 Jan 15;47(2):467–71.
[18]. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. IARC Working Group. Lyon, 23-30 October 1984. IARC Monogr Eval Carcinog Risk Chem Hum. 1985 Sept;37:1–268.
[19]. Shieh TY, Yang JF. Collagenase activity in oral submucous fibrosis. Proc Natl Sci Counc Repub China B. 1992 Apr;16(2):106–10.
[20]. Ma RH, Tsai CC, Shieh TY. Increased lysyl oxidase activity in fibroblasts cultured from oral submucous fibrosis associated with betel nut chewing in Taiwan. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 1995 Oct;24(9):407–12.
[21]. Tsai CC, Ma RH, Shieh TY. Deficiency in collagen and fibronectin phagocytosis by human buccal mucosa fibroblasts in vitro as a possible mechanism for oral submucous fibrosis. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 1999 Feb;28(2):59–63.
[22]. Jeng JH, Chang MC, Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. Oral Oncol. 2001 Sept;37(6):477–92.
[23]. Trivedy CR, Warnakulasuriya KA, Peters TJ, Senkus R, Hazarey VK, Johnson NW. Raised tissue copper levels in oral submucous fibrosis. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2000 July;29(6):241–8.
[24]. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN. Oral submucous fibrosis: study of 1000 cases from central India. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2007 Jan;36(1):12–7.

[25]. Kiran Kumar K, Saraswathi TR, Ranganathan K, Uma Devi M, Elizabeth J. Oral submucous fibrosis: a clinico-histopathological study in Chennai. Indian J Dent Res Off Publ Indian Soc Dent Res. 2007;18(3):106–11.

[26]. Babu S, Bhat RV, Kumar PU, Sesikaran B, Rao KV, Aruna P, et al. A comparative clinico-pathological study of oral submucous fibrosis in habitual chewers of pan masala and betelquid. J Toxicol Clin Toxicol. 1996;34(3):317–22.

[27]. Shah N, Sharma PP. Role of chewing and smoking habits in the etiology of oral submucous fibrosis (OSF): a case-control study. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 1998 Nov;27(10):475–9.

[28]. Ahmad MS, Ali SA, Ali AS, Chaubey KK. Epidemiological and etiological study of oral submucous fibrosis among gutkha chewers of Patna, Bihar, India. J Indian Soc Pedod Prev Dent. 2006 June;24(2):84–9.

[29]. Bhowate RR, Lohe VK, Meshram MG, Dangore SB. Serum aflatoxin B1 antibody titer, percent hemolysis and transaminases in oral submucous fibrosis. J Oral Maxillofac Pathol JOMFP. 2021;25(1):110–7.

[30]. Choube: Betel-nut-induced oral lichenoid lesion in... - Google Scholar [Internet]. [cited 2025 Nov 27]. Available from: https://scholar.google.com/scholar_lookup?journal=J%20Indian%20Acad%20Oral%20Med%20Radiol&title=Betel-nut%20induced%20oral%20Lichenoid%20lesion%20in%20oral%20submucous%20fibrosis%20and%20its%20relation%20with%20liver%20enzymes%20and%20hepatitis%20C%20virus-ribonucleic%20acid&author=SH%20Choube&author=RR%20Bhowate&volume=30&publication_year=2018&pages=265-70&

[31]. Risk of betel quid chewing on the development of liver cirrhosis: a community-based case-control study - PubMed [Internet]. [cited 2025 Nov 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/17448681/

[32]. Wu GHM, Boucher BJ, Chiu YH, Liao CS, Chen THH. Impact of chewing betel-nut (Areca catechu) on liver cirrhosis and hepatocellular carcinoma: a population-based study from an area with a high prevalence of hepatitis B and C infections. Public Health Nutr. 2009 Jan;12(1):129–35.

[33]. Sarma AB, Chakrabarti J, Chakrabarti A, Banerjee TS, Roy D, Mukherjee D, et al. Evaluation of pan masala for toxic effects on liver and other organs. Food Chem Toxicol Int J Publ Br Ind Biol Res Assoc. 1992 Feb;30(2):161–3.

[34]. Shieh DH, Chiang LC, Shieh TY. Augmented mRNA expression of tissue inhibitor of metalloproteinase-1 in buccal mucosal fibroblasts by arecoline and safrole as a possible pathogenesis for oral submucous fibrosis. Oral Oncol. 2003 Oct;39(7):728–35.

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 122-128 www.ijdmsrjournal.com
ISSN: 2582-6018