Tobacco Addiction: Effect on Human Health

Chapter 6

Tobacco Chewing/Smokeless Tobacco: It's Effect on Human Health

Malti Kumari Maurya*; Rana Pratap Maurya[1]

[1]Department of Orthodontics and Dentofacial Orthopedics, Babu Banarasi Das College of Dental Sciences; Babu Banarasi Das University, Lucknow, U.P. India

***Correspondence to: Malti Kumari Maurya,** Department of Pathology, King George's Medical University, U.P. Lucknow, India, 226003*

Email: mauryamalti@yahoo.co.in

Introduction

Tobacco is a powerful addictive substance which is deliberately consumed all over the world. People enjoy tobacco and its products via various methods in different parts of world. It is consumed either orally by *smoking* through cigarettes, pipes, cigar, bidi, hukkah, chhutta etc. or *chewed* in the form of raw leaves as khaini; or altered form as pellets, plugs, gutkha/ pan masala and snus/dripping or e-cigarettes. It is also taken (sniffed) through nasal route as nasal snuff (luktsnus). Chewing/Smokeless tobacco is consumed with or without flavouring agents and sweeteners [1,2]. In this method tobacco product is placed between cheek and gums or lower lip and teeth. Then it is slowly chewed or crushed to release flavour and nicotine and unwanted juices are expectorated at short intervals till the content finishes. So, it is also known as spitting tobacco.

In South-east Asia region smokeless/chewing tobacco is a very popular habit among all the age groups. It is popularized due to easy availability of various substitutes of smokeless tobacco like chaini-khaini, lozenges (mouth freshners), zarda, pan masala, gutkha, mishri and gul etc.The famous product pan masala/gutkha is a mixture of tobacco, areca nut, slaked lime, catechu, flavouring agents and condiments [3,4]. In the last few decades small attractive and inexpensive sachets of gutkha and pan masala have been aggressively advertised and marketed by various companies and often claimed to be safer product. These products yield popularity among all ages of male, female and even in school going children particularly in India. Tobacco contains various chemicals among which alkaloid nicotine is a stimulant and highly ad-

dictive substance even in lesser dosage hence, it easily makes a customer; a loyal consumer. In addition to nicotine, smokeless tobacco products contain over 30 carcinogens [1]. These products have been strongly implicated in the recent increase in the incidence of oral cancer,head and neck cancer, oral submucous fibrosis and other oral diseases in very young population in South-East Asia region [1-3]. Since gutkha, pan masala and other tobacco products are mixture of several ingredients, hence carcinogenic potential is further accentuated. Additionally, these products are potently addictive and enhance early dependence.

Types of Smokeless Tobacco and its Products

Smokeless tobacco is that form of tobacco where it does not burn and use by other means than smoking. It is also known as chewing tobacco, oral tobacco, spit or spitting tobacco, dip, chew, and snuff. Now spitless, smokeless tobacco has also been developed in some countries. In South-east Asia region, use of smokeless tobacco is a threat for public health in many countries. Various types of ready to use smokeless tobacco products like pan masala, panbahar, gutkha, mawa, gul,mishri, zarda etc are manufactured and marketed with different brand names. For ease of the customer, it is packed in various sizes tin cans, plastic packets or individual dose of small pouches/sachets and are available widely at every place like city, town, villages, railway station, bus stop, retail shops, small road side venders, street or footpath. School going children and other people easily get attracted towards these cheaper, scented and small fancy sachets/ pouches of tobacco products. Initially they start curiously as time pass or for fun or as mouth freshener and gradually get addicted to it. Various types of smokeless tobacco and its products used worldwide are:

1. Khaini (India): Chewing raw tobacco leaves is the oldest method of consuming tobacco. It is consumed either as whole sweetened dry leaves or in shredded form with lime. Small amounts are placed in the vestibule of lip or between the gums and teeth, where it is gently crushed or rolled to release the content and nicotine. It stimulates the salivary glands, which leads to the development of the spittoon and is discarded periodically. Chewing tobacco is now modernized as several varieties of products like *scrap* (most often as loose leaves), *pellets* (tobacco bites or bits), *plug* (a form of loose leaf tobacco condensed with a binding sweetener) and *twist* (rope-like piece of tobacco twisted together). Nearly all modern chewing tobacco products are produced via a process of leaf curing, cutting, fermentation and processing or sweetening [1-6].

2. Paan/ betel quid: Paan is famous preparation used in South East Asia region. It is prepared by combining betel leaf with areca nut (seed of areca palm), katha, slaked lime, sweetener, mouth freshener and tobacco **[Figure-1]**. The compiled mixture is wrapped / rolled nicely with betel leaf and placed in mouth **[Figure-2]**. Ingredients vary in different regions and the preparation is named accordingly [7-9]. Paan is chewed for its stimulating and psychoactive

effects. After chewing, it produces red colour saliva which is either swallowed or spat out. In India people discard spit leniently here and there which creates unsightly atmosphere.

3. Guṭkha/pan masala/ pan parag/ mawa: It is ready to use preparation of crushed areca nut, tobacco, catechu (extract from the wood of the acacia plant), paraffin wax, slaked lime, sweetener and condiments or savory flavourings **[Figure-3A-C]**. The final mixture is packed with different brand names which have slight difference in their ingredients. It is light brown to whitish coarse powdery mixture which immediately dissolves in mouth after consumption and produces sweet and very pleasant flavour and red coloured saliva. It is largely manufactured in India and exported and sold across South Asia in small, low cost, individual-sized/sachets/ packets. These are widely consumed by all age groups and all strata people in countries like India, Pakistan and Bangladesh, Nepal, Bhutan, Sri Lanka etc [2,9-10].

4. Gul, mishri, or gudahku: It is a toothpaste/tooth powder like preparation which is applied on teeth and gums. It is used mainly in India and Bangladesh. People from rural areas uses these products at a higher rate than urban residents [2,11].

5. Dissolvable tobacco: It is finely ground tobacco that is pressed into shapes such as orbs, lozenges, tablets, sticks or strips which slowly dissolve in the mouth. These products appeal to adolescent because they come in attractive packaging, look like candy or small mints, that can be easily hidden.

6. Toombak and shammah: It is mixture of tobacco, slaked lime and ash and taken orally. These products are mainly consumed in north and eastern Africa and the Arabian Peninsula [2].

7. Zarda: It contains shredded tobacco leaves, boiled with lime and spices. This mixture is dried and coloured with vegetable dyes and then mixed with finely chopped areca nuts. It is used alone or with betel leaf in India and Arabian countries [**Figure-3B** and **D**] [2,7].

8. Naswar: It is a mixture of tobacco, slaked lime, indigo, cardamom, oil and menthol. Used as powdered form or water is added to make roll or balls. It is mainly used in Iran, Afghanistan, Pakistan, India and Central Asia [2,11].

9. Snuff: It is a dissolvable form of smokeless tobacco which is more prevalent in the United States. It is finely ground form of tobacco that can be dry, moist, flavoured and packaged in small tin cans, packets or pouches [7-8]. It can be consumed through various routes. Dry (fire-cured) powder form is put in the mouth or inhaled through the nose whereas moist form (age cured) is fermented tobacco processed into fine particles is placed between cheek or lip and gums and requires spitting. Other form is U.S Snus, originated in Norway and Sweden which comes in small tins. It is a non-fermented steam-pasteurized moist powdered tobacco product.

These are available in ready-to-use pouches that are placed between cheek or teeth and gums and do not require spitting.

Incidence of Smokeless Tobacco

The popularity of smokeless tobacco is growing rapidly and its prevalence of use is rising all around the world. People think that smokeless tobacco products are less harmful alternative to smoking, but it hurts and kills the people all the same. Smokeless tobacco and their products are used in a wide variety of forms and available worldwide in many countries of the world [12,13]. It contains many toxic chemicals and carcinogens, which causes negative health effects and deadly cancer. Due to widespread advertisement and exhaustive marketing of smokeless tobacco products, school children and young population are attracted more towards this bad addictive habit.

Smokeless tobacco use is a global problem that is present in low, middle and high-income countries and affects more than 300 million people. The greatest burden of smokeless tobacco use is in the South-East Asia which experiences the highest prevalence including 89% of the world's users [**Figure- 4**]. It also carries the highest attributable disease burden, and has the different varieties in smokeless tobacco product and forms of its use. According to WHO (2009), tobacco consumption has been increasing at the rate of 2% to 5% per year. It is estimated that number of deaths due to tobacco will increase from 3 million per year worldwide to 70 million per year by 2025 [13-17]. Prevalence of tobacco use in worldwide are as follows:

1. Asia: In the 11 countries of the WHO South-East Asia Region (SEAR), around 250 million adults consume smokeless tobacco which constitutes approximately 90% of global smokeless tobacco users. Its prevalence among youth and adults is higher in males than females. However, WHO estimates show that smokeless tobacco use among females in south Asia is a major public health threat. Among females, Bangladesh (27.9%) had the highest prevalence of smokeless tobacco consumption, followed by India (18.4%), and Bhutan (17.3%). Among males, Myanmar **(51.4%)** had the highest consumption rates of it followed by Nepal (37.9%), India (32.9%), and Bangladesh (26.4%) **[Figure- 5]** It is lowest in China (0.4%) [1,2,16-21].

India has one of the highest tobacco users in the world in number, diversity in product types and forms of smokeless tobacco. It is the only country in the world where overall smokeless tobacco (26%) use is nearly twice as prevalent as smoking (14%) [17-18]. There are more than 30 different types of smokeless tobacco products are available including zarda, gutkha, gul, mishri, betel quid, mawa, pan masala etc. Beside this, people make their own chew by mixing ingredients like zarda, areca nut, lime, spices according to their taste. Due to the extraordinary rate of consumption of smokeless tobacco products in north India, prevalence of oral cancer is high especially in Uttar Pradesh. In India these products are also famous among children and teenagers. It has been reported that 40% of school students and 70% of college

students regularly chew gutkha in Mumbai [14,18,22-25].

2. Europe: Smoking is more prevalent than smokeless tobacco (ST) in Europe. They consume ST mainly as moist snuff, snus, chewing tobacco (twist) and e-cigarettes. Prevalence of ST use among adults varies from 0.1% in Maldova 3% in Denmark, 4% in Switzerland to 24% in Sweden and 31.8% in Uzbekistan. Men have higher rates of ST use than women. In Scandinavia, Swedish snus, a particular type of moist snuff product, is very famous. But immigrants from SEAR show higher rate of ST use and specially consume their traditional products like pan masala and gutkha. In Kyrgyzstan and Uzbekistan, naswar is used, which is similar to the product known as nass or naswar in Iran and Pakistan [1,2,11].

3. American region: In USA smokeless tobacco use is low (average 3.4%). It is used in two forms: chewing tobacco and snuff or snus. Approximately 6.7% of U.S. male and 0.3% female adults uses smokeless tobacco. It is highest in Wyoming (9.1%), West Virginia (8.5%), and Mississippi (7.5%), and lowest in California (1.3%), Columbia (1.5%), Massachusetts (1.5%) In North America, moist snuff is the most widely used product. [1,26-27].

4. African region: Prevalence of smokeless tobacco use and types of products varies across countries. They are sniffed, chewed, sucked, or applied to teeth and gums. ST prevalence is as high as 28.3% for females vs 5.7 % males in Mauritania and 22.6% for males vs 19.6% females in Madagascar, 21.0 % for males vs 0.4% females in Algeria and as low as 0.3% for males vs 1.2% females in Zambia and1.3% males vs 0.2 % females in Ghana [1,2,18].

Youth: The findings of the Global Youth Tobacco Survey show that the overall tobacco consumption especially among students, has not decreased in most of the countries; rather, it has shown an increasing trend and noted very high in SEAR and Africa region. The current rate of use of any form of tobacco products among boys ranges from 8.5% (Maldives) to 54.5% (Timor-Leste) while 3.4% (Maldives) to 29.8% (Timor-Leste) among girls.

Africa, Eastern Mediterranean and European Region; For smokeless tobacco use in boys (13-15 yrs), prevalence was highest at 18.3% in Congo and lowest at 1.1% in Montenegro and for girls (13-15 yrs), prevalence ranged from 15.8% in Namibia to 0.7% in Serbia. Total ST use prevalence was high (more than 10%) in 5 countries; Botswana11.3%, Djibouti 12.6%, Lesotho 14.4%, Namibia 16%, and Congo 16.4%.

Prevalence of current smokeless tobacco use among students boys aged 13-15 years in SEAR is varies from 5.8% in Bangladesh to 14.1% in India and use of smokeless tobacco products among **girls** aged 13-15 years ranges from 2.3% Thailand to 6% India [16-23].

In U.S.A smoking habit has declined among high school children but use of smokeless tobacco has sharply increased in duration 2011-15 from 1.5 to 15% (highest for e- cigarettes)

Recently, in 2015 CDC (Centers for Disease Control and Prevention) report it was 10% in high school boys and 1.8% in high school girls [28-29].

Side Effects of Smokeless/Chewing Tobacco on Oral Health

It is a common belief that smokeless tobacco is safer alternative to smoking tobacco or it may be more conveniently used anywhere which also been emphasized by many advertising popular models or companies. Some people start use of smokeless tobacco as toothache remedy or in form of tooth powder or paste. In developing countries adolescents start chewing tobacco products specially pan masala/ gutkha/ mawa just curiously or as a time pass or as mouth freshener, as these products are easily available at general store/retail shops or even road side vendors on footpath **[Figure- 6 and 7]**. Sometimes, young girls start use of smokeless tobacco as a means to lose or control weight. Whatever the reason maybe, tobacco is enjoyed by all age groups worldwide. It is a pity that they are unaware of dangerous consequences or toxic properties of tobacco products.

Toxins in smokeless tobacco

It has been estimated that tobacco, and smokeless tobacco products, contain roughly 4,000 chemical constituents, including nicotine and other toxicants and over 30 carcinogens (substances which have potential to cause or promote cancer) which are believed to play a crucial role in causing the negative health effects besides addiction [30,31,32].

International Agency for Research on Cancer (IARC) documents that traditional smokeless tobacco as well as altered/refined products, such as snuff, chewing tobacco, and betel quid, pan masala, gutkha, mawa, etc. are carcinogenic to humans. It is also found that smokeless tobacco products cause precancerous oral lesions and cancers of the oral cavity, oesophagus, and pancreas as well as reproductive and developmental toxicity [1,6,33]. Smokeless tobacco products differ considerably in their concentrations of nicotine and volatile and non-volatile nitrosamines and other contents because it passes through various steps like tobacco processing, curing, fermentation and storage during manufacturing. Each step is differed for variety of products or treatment with chemicals which impart formation of toxic substances.

All smokeless tobacco products contain nicotine, and virtually all contain tobacco-specific nitrosamines (TSNAs). Other substances are variable in different tobacco products including N–nitrosamino acids, volatile N–nitrosamines, polycyclic aromatic hydrocarbons (PAHs), volatile aldehydes, inorganic compounds, heavy metals, metalloids and radioactive metals [1,31,34,35]. TSNAs and PAHs are carcinogenic to humans. TSNAs include 5-6 chemicals of which N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)1-butanone (NNK) are most toxic and IARC classify them as Group 1 carcinogens [36-38] *[group-1 carcinogen: means substance is a proved carcinogen in animal models]*. The nitrosamines can be

metabolized in human body by target tissues to compounds that can modify cellular genetic material. This alteration can be repaired to some extent but if chronic modification occurs, it leads to mutagenesis/ carcinogenesis (initiation of cancer formation) **Toxic metals** that have been found in ST products include arsenic, beryllium, chromium, cobalt, cadmium, lead, nickel, mercury, and the radioactive metals polonium-210 and uranium [36,39].

Tobacco products also contain added plant materials such as tonka bean or sweetener, flavouring agents that may further contribute to adverse health consequences. Areca nut containing products like paan (betel quid), gutkha, tombol, pan masala and mawa, are commonly used in South-East Asia, Middle East, South Africa and other parts of the world. [7,17]. Areca nut itself is considered by an IARC as group 1 carcinogen and has been associated to oral submucosal fibrosis (OSF) and oral squamous cell carcinomas. Therefore, the health risks associated with smokeless tobacco can vary with use of products, manner and duration of use. When tobacco is mixed with other chemicals or substances with a carcinogenic potential its deleterious effect synergizes [1,9,40-41].

Mechanism of cancer induction

Mechanism of cancer induction in smokeless tobacco users is shown in **[Figure-8]**. Genotoxic effects occur from smokeless tobacco and its products like paan and gutkha mostly due to the presence of nitrosamine, its compound and heavy metals. The nitrosamine in the chewers' saliva undergoes nitration when it reacts with nitrite in the presence of a catalyst [1,43]. The nitrosamine in tobacco and its products undergoes metabolic activation by cytochrome P450 enzymes. It leads to the formation of N-nitrosonornicotine (NNN), methylnitrosaminobutanone (NNK), methyl-nitrosaminopropionitrile (MNPN) Arecoline and Reactive oxygen species (ROS) which are major carcinogens [9]. These substances further leads to DNA damage or methylation. If this damage is not repaired, causes permanent DNA mutations, such as in the RAS oncogene or the TP53 tumor suppressor gene, leading to uncontrolled cell growth and ultimately cancer. Other mechanisms that may contribute to cancer promotion include chronic local inflammation and irritation, oxidative stress, and reactive oxygen species [11,44].

Adverse effects

Smokeless tobacco users generally keep crushing the contents in oral cavity for a long duration while chronic users may even keep for a full day. The contents of tobacco mixed with saliva; are slowly absorbed through oral mucosa and may also cause local irritation and sensitization. Contents which are absorbed through the oral mucosa and by swallowing saliva (containing nicotine, sweetener, flavour and various toxic substances) reach the systemic circulation. In this way these harmful chemicals (carcinogens and other toxicants) circulate throughout the body and may induce cancer and damage to multiple organs [42-44].

Little et al in their study compared 245 smokeless tobacco users and 223 non-smokeless tobacco users with same age distribution and found that 78.6% of smokeless tobacco users had observable oral lesions as compare to 6.3% of non-smokeless tobacco users. 85% of the lesions in smokeless tobacco users were located in the primary area of tobacco placement [45].

The adverse effects of using smokeless tobacco or chewing tobacco or their ready-made products can be *local or systemic*:

A. Local: In the oral cavity its effect is on both soft and hard tissue; including teeth, supporting ligaments and temporo-mandibular joint. Soft tissue includes mucosa and submucosa which is delicate covering of entire oral cavity. Oral mucosal lesions are more severe in people who use smokeless tobacco and its products at an earlier age or for longer duration per day or greater dosages or on more days per month or for years [6]. The benign (precancerous) lesions usually resolve when people stop using tobacco.

B. Systemic: Effects on distant organs of the body.

[A] Local effects on soft and hard tissues of oral cavity

1. Staining of teeth: Most common effect of chewing tobacco/paan is reddish brown staining/ discolouration of teeth and oral mucosa [46]. Tobacco users lose their sparkling smile **[Figure-9]**. It is caused by various ingredients like betel nut and catechu mixed with lime and other substances. Initially the staining is temporary, but as the user becomes habitual, staining becomes permanent. In India and South-East Asia, the use of pan masala, gutkha and betel nut is so familiar that people do not bother to have coloured tooth and oral mucosa. They do not even hesitate to spit on the public places, official places, streets, lifts and stairs.

2. Betel chewer's mucosa: The oral mucosa at site of placement of betel quid (paan) and areca nut becomes loose and irregular with desquamated tags of tissue and underlying areas can also show wrinkled appearance. This condition may be caused due to either direct action of the betel quid or traumatic effect of chewing or both. This leads to tendency for the oral mucosa to desquamate or peel off. The affected areas also show the evidence of incorporation of ingredients of the betel quid in the form of yellowish or reddish-brown encrustations. Betel chewing produces reactive oxygen species (ROS) that is detrimental to oral mucosa and cause damage to lining epithelial cells.

The lesion is often localized and strongly associated with the habit of betel nut/paan chewing for long durations. The chewer's mucosa usually develops at age of 50 years or more after chronic use [47-48]. Several studies have shown that the prevalence of betel chewer's mucosa may vary between 0.2 to 60.8% in different south East Asian populations. Betel chewer's mucosa is not potentially a precancerous lesion but this condition is often co-exists with

other mucosal precancerous lesions such as leukoplakia and oral submucous fibrosis [49-50].

3. Gingival and Periodontal diseases: Due to continuous use of smokeless tobacco for long duration, the hygiene of oral cavity becomes poor which leads to development of many oral problems. Chemicals and toxins that are present in smokeless tobacco and their products make the chewer so addictive and with each chew it irritates the gum tissue and periodontium. It also abrades gingival surface causing it to pull away from teeth (gingival recession) and makes the gingiva more prone to gum diseases like gingivitis, periodontitis etc. Incidence of gingival recession is commonly seen adjacent to the area where the tobacco is held. It is higher among individuals who use snus or snuff than people who do not use smokeless tobacco. Gingival recession can be observed within one year of beginning to use smokeless tobacco [1,6, 50-53].

4. Dental caries and Tooth loss: It is common belief that chewing areca nut is protective for tooth as it contains anti-bacterial properties but in long term it rather harms. Prevalence of dental decay and caries is more associated with the use of chewing tobacco. [54] When the gingival tissue pulls away (gingival recession) it creates greater risk for tooth decay. The ingredients present in ready to use tobacco products like tobacco, areca nut, catechu and slaked lime (calcium hydroxide) together may cause greater inflammation and injuries than one of these ingredients used alone. [55] Sugars are often added to enhance sweetness and flavour of smokeless tobacco, acts as nutrient medium for growth of microorganisms and hence increase the risk for tooth decay. Grit in betel nut or gutkha causes abrasion of hard coating of teeth (enamel) leading to sensitivity to hot or cold and individual feel pain on taking cold or hot food materials. Gradual abrasion also causes shortening of tooth and eventually tooth loss **[Figure 10]** [47,48,52].

5. Root fracture of tooth: Smokeless tobacco products contains some gritty and hard substances like betel nuts, so in chronic users there is risk of root fracture of tooth, trismus and other pathology of temporomandibular joint [47,56].

6. Bad Breath: Long-term use of smokeless tobacco causes bad breath or halitosis due to production of nicotine and other chemicals in their mouth and thus allows bacterial growth resulting in bad breath. Moreover, due to the habit of continually spitting, saliva gets exhausted leading to dry mouth and person deprived of the protective antibacterial property of saliva. This leads to infection or other harmful consequences [51,57].

7. Alteration of taste and smell: Chewing tobacco alters person's sense of taste and ability to smell. As a result, tobacco users like to eat saltier and sweet foods which are harmful if consumed excessively [51,54, 57].

8. Nasal Problems: Some types of ST are inhaled nasally like dry (powdered tobacco) snuff, can cause edema of the mucosa and submucous connective tissue of the turbinates, atrophy

of the middle and inferior turbinates, reduction of nasal mucociliary clearance, and chronic rhinitis.

9. Development of Pre-Malignant Lesions of Oral Cavity

In smokeless tobacco chewers, the hygiene of oral cavity becomes poor day by day with gradual loss of saliva which leads to many oral problems. In the chewer's mouth, the tobacco contents and its toxins mixed with saliva remain in contact with oral mucosa for long duration, causing staining and deleterious effects like desquamation, non-healing ulcer and thickening of mucosa. Gradually these changes progress to precancerous lesions like white patches (leukoplakia), red sores (erythroplakia), tobacco pouch keratosis, quid induced lichenoid reaction, oral submucus fibrosis, tobacco associated melanosis etc. These harmful effects are so gradual in onset that tobacco user can not relate the tobacco as a causative agent and they become so addicted to tobacco that they don't want to give up the habit even on these warning signs and on doctor's advice.

Several studies from the United States, Europe, and Asia provide conclusive evidence that smokeless tobacco products, including snus, snuff, shammah, and betel quid (paan), are strongly associated with the prevalence of oral mucosal lesions such as leukoplakia, erythroplakia, and verrucous hyperplasia and have risk to transform into cancer. [1,9,40-41,43] These mucosal lesions are more severe in those persons who start chewing ST products at an earlier age and use for more hours per day, use greater dosages, or use on more days per month [6].

Tobacco chewing leads to development of various pre-malignant (precancerous) lesions which are:

1. Oral sub mucus fibrosis (OSMF): It is a chronic, insidious onset, potential malignant lesion of the oral cavity, caused by chronic use of areca nut/paan. It is characterized by inflammatory and progressive fibrosis of the submucosal tissues, leading to restricted mouth opening or (stiff mucosa). As the disease progresses, the jaws become so rigid that the person is unable to open the mouth or eat food. It may affect the entire oral cavity or may extend to the pharynx. In India, the prevalence OSMF increased over the past four decades from 0.03% to 6.42% [58].

a. *Clinical feature*: OSMF is characterized by sunken cheeks, thin stiff lips, dryness and burning sensation of the oral mucosa followed by ulceration pain, and change in tone of voice. The oral mucosa also shows a mottled marble like appearance with thick vertical fibrous bands. These bands restrict the mandibular range of motion and causes trismus. So, in these patients maintenance of oral hygiene becomes poor, dentition often is stained as a scarlet colour and develops gingival and periodontal diseases **[Figure-11]**. Condition of patient is extremely debilitating and has a high risk of transformation into the oral cancer. A malignant transformation

rate of 7.6% over a period of 10 years was described in an Indian cohort [59].

b. Aetiology: Various factors have been implicated in the development of OSMF; the most common of which is chewing betel nut or tobacco products like pan masala, gutkha, mawa etc. Other causes are autoimmune reaction, vitamin and iron deficiency have been reported [47-49,60-63].

c. Pathogenesis: Recently suggested pathogenesis of OSMF is by action of betel nut and its toxic chemicals which leads to gradual deposition of collagen in submucosa **[Figure 12]**. The alkaloids present in betel/areca nut, arecadine arecoline and guvacine which have psychotropic properties. Among these, arecoline (active metabolite) is the main agent which causes stimulation of fibroblasts leading to proliferation and collagen synthesis. It results into excessive amount of collagen deposition. In addition, repeated trauma to mucosa by grit, or chewing areca nut or grit in pan masala, induce inflammation which release various collagen stimulating and stabilizing cytokines and growth factors like transforming growth factor-β (TGF- β), platelet derived growth factor (PDGF) and fibroblast growth factor (FGF). Also, tannin and copper present in areca nut further enhance collagen fibers deposition. Interferon-α is decreased which has anticollagen property. All these mechanisms finally result into fibrosis of oral mucosa termed as OSMF [47].

d. Incidence: OSMF is very common in South-East Asia but has started to spread to Europe and North America due to increasing the widespread habit of pan and gutkha use. The current prevalence of smokeless tobacco use is very high in India. India (32.9% males) which have been strongly implicated in the recent increase in the incidence of oral submucous fibrosis, especially in the very young / adolescents, even after a short period of use [11]. Kumar BN et al found in his study that OSMF is highly prevalent in smokeless tobacco users as compared to conventional and reverse smokers [47,64-65].

6. Prognosis and treatment: It depends on the degree of clinical involvement. Most of the patients with OSMF presents with moderate-to-severe stage. If OSMF is diagnosed at a very early stage, it is reversible with cessation of tobacco chewing habit alone. Moderate OSMF is reversible with cessation of habit along with some medications and mouth opening exercises whereas severe oral submucous fibrosis is irreversible and potential to develop into malignancy.

2. Leukoplakia: It is a thick and firmly attached white patch or plaque that can be found on oral mucosa, gingiva, tongue, palate, floor of mouth and pharynx. The patch may appear translucent or opaque and raised or ulcerated **[Figure-13]**. Leukoplakia is a clinical term hence other disease must be ruled out by doing tissue biopsy of lesion and its histological examination. Leukoplakia changes with time and progress to more severe lesion.

a. Aetiology: It is caused by chronic irritation due to tobacco chewing, smoking, alcohol and betel nut. Other causes may be sharp cusp of teeth or ill-fitting dentures. It usually occurs at middle age (after 30 years).In India many studies have proven that leukoplakia is strongly associated with smokeless tobacco and areca nut use and seen in young adults and adolescents[51,61,64, 66-68].

b. Type of leukoplakia: There are various types of leukoplakia recognized according to appearance like homogenous, non–homogenous, flat or raised, nodular and exophytic. Verrucous leukoplakia (or verruciform leukoplakia) is type of leukoplakia appear as thick, white, papillary lesions [47-48,69].

c. Risk of malignancy: The prevalence and severity of leukoplakia show a dose-response relationship, which is best predicted by the amount, frequency and duration of smokeless tobacco or betel nut use [66,68-69]. *Author* Warnakulasuriya reviewed four case control studies that showed relative risk of oral leukoplakia in betel quid (paan) chewers. They found that chewing areca (in betel quid without tobacco) raised the odds ratio (OR) to 5 compared with non-chewers (OR=1); adding tobacco to the quid further raised the relative risk by at least three-fold compared with non-tobacco users [67].

Leukoplakia is a pre-step of cancer, that gradually progresses to oral dysplasia (disorganised cells but limited to oral epithelium) to frank cancer (squamous cell carcinoma) **[Figure 14]** [70-71]. Various studies have examined the transformation rates of oral leukoplakia to cancer. Pindborg et al [72] followed 248 patients for a mean period of 3.7 years; during this period prevalence of malignant transformation in leukoplakia was found 4.4% whereas Banocz and Csiba reported 6% transformation in their study of 670 patients observed over a period ranging from 1 to 30 years [73]. **Erythroplakia:** Erythroplakia is also a clinical term which appears as a red patch/eroded area. It occurs most commonly on the floor of the mouth. Biopsy is required to see the degree of atypical changes in oral mucosa or to exclude oral cancer. There may be mixed lesion white and red patch termed as erythro-leukoplakia.

d. Prognosis: Majority of oral leukoplakia lesions behave benign and often regress after stoppage of smokeless tobacco product or irritating agent. [74] But total response is un-predictable; it also depends on degree of associated dysplasia, duration, frequency and type of tobacco product used. Verrucous or nodular lesions, red lesions (erythroplakia) and mixed red and white lesions (erythro-leukoplakia) have a higher risk of cancerous change than homogenous leukoplakia [75].

3. Tobacco pouch keratosis: It is a focal, ill-defined area of white patch which develops at the site where tobacco chewers placed the tobacco each time. Most commonly, it involves the mandibular labial and buccal mucosal folds. The continued use of tobacco causes the affected areas to become opaque white and corrugated. Microscopically, tobacco pouch keratoses show

hyperkeratosis and acanthosis of the mucosal epithelium. But epithelial dysplasia is uncommon and if present usually mild type [76]. The condition usually disappears once the tobacco habit is stopped. It is associated with slightly increased risk of mouth cancer [77].

4. Betel quid/Areca nut induced lichenoid reaction: Areca nut is group I carcinogen and is one of the culprit to cause oral cancer in smokeless tobacco users. Areca nut also causes various precancerous to cancerous lesion of oral cavity. Areca-induced lichenoid lesions are mainly seen at the sites of quid application like buccal mucosa and tongue. [48] It is seen as fine wavy keratotic (white) lines/striae which are radiating from a central red/atrophic area. These lines do not criss-cross and are parallel to each other. The histological picture shows hyperkeratosis. The lesion usually resolves following cessation of areca use.

5. Proliferative Verrucous Leukoplakia (PVL): It is a clinical term and previously was termed as oral florid papillomatosis. It is a rare form of oral leukoplakia (non-homogeneous type) which is irreversible, slow growing with highest potential of malignant transformation and resistant to treatment. It starts initially as a white plaque of hyperkeratosis that eventually becomes a multifocal disease with confluent, exophytic, papillary and proliferative features.

Aetiology of PVL is uncertain but some viruses and tobacco association is described by some authors [78,79]. Biopsy examination of such lesions may show spectrum of histopathological lesions from simple hyperkeratotic lesion to verrucous hyperplasia or verrucous carcinoma or verrucous hyperplasia with dysplasia or well differentiated squamous cell carcinoma. The buccal mucosa, gingiva, and alveolar ridges were most commonly affected sites. The average age of presentation of PVL is above 60 years and more common in women. Risk of malignant transformation is highest which can range between 60-100% [79-80].

Malignant lesions of oral cavity developed due to areca nut/tobacco chewing: Areca nut/ tobacco consumption can also lead to development of various malignant lesions which are as follows:

1. Verrucous carcinoma (VC): It is a rare warty variant of squamous cell carcinoma frequently seen in smokeless tobacco chewers or those who frequently use snuff orally; hence it is sometimes referred to as “Snuff dipper’s cancer. Histologically verrucous carcinoma shows keratotic exophytic surface comprising of sharp/blunt hyperplastic epithelial projections with keratin plug and also these projections pushing downward into sub-epithelial tissue. It behaves as locally invasive tumour and rarely metastasizes. Clinically, these tumors present as, slow growing, painless, white-gray, warty lesions. It should be differentiated carefully from close simulating benign and malignant lesions like verrucous hyperplasia/ proliferating verrucous leukoplakia, well differentiated squamous cell carcinoma. It is commonly seen in men over the age of 65 years. It most commonly affects the buccal, gingival and alveolar mucosa hard palate, floor of the mouth, larynx but any oral segment can be affected. Secondary infections

are frequent, and may lead to an unpleasant odor and reactive lymphadenopathy [81].

Aetiology: Various causative factors have been suggested for verrucous carcinoma and Human Papilloma Virus (HPV) has been considered one of them. [82] Smoking tobacco is highly associated with the development of mucosal verrucous carcinoma of the head and neck while poor oral hygiene, presence of oral lichenoid and leukoplakic lesions may act as enhancing effect. In Asia it has also been found that leukoplakia has a synergistic effect which is associated with smoking, and chewing tobacco habits. [62] Shear and Pindborg in their study reported that out of 28 patients with verrucous lesions, 24 (86%) used tobacco and one was an areca quid chewer [83]. Chen et al in a study found that tobacco appears to be a major factor in causation of verrucous lesions [84]. In Taiwan, a study of verrucous carcinoma, areca quid chewing was reported 97.3% of cases [85].

Prognosis: Most patients with verrucous carcinoma have a good prognosis. Surgical excision or laser therapy is possible treatments.

2. Oral intraepithelial dysplasia: These lesions denote the various stages of cancer progression from initial to invasive form and can be associated with long standing premalignant conditions like leukoplakia, erythroplakia, oral submucous fibrosis, PVL etc. Clinically, this may look like above premalignant entities or with some atypical changes within them as ulceration, bleeding, rapid change in shape and appearance or pain. In these cases diagnosis and management of lesions should be decided by histopathological examination (HPE). In epithelial dysplsia, there is disorganisation and abnormal proliferation of epithelial cells; if they remain within boundary of epithelium it is term as intra epithelial dysplasia when these abnormal proliferating cells cross the boundary and goes into underlying subepithelial loose tissue it is termed invasive tumor/squamous cell carcinoma (SCC).

3. Oral squamous cell carcinoma: It is most common cancer of oral cavity and accounts for 90% of all oral cancers. Oral cancer ranks the eighth position in the cancer incidence ranking worldwide and in India it ranks third most common malignancy [86-88]. Along with cancers in the head and neck region; it is one of the leading causes of death in developing countries of South East Asia [89]. *Aetiology:* Smokeless tobacco is one of the major risk factors associated with the high prevalence of head and neck and oral cancer in this region. It is estimated that over 90% of the global smokeless tobacco use burden is in South East Asia. [16,17] In a systemic meta-analysis Khan et al reported that the pooled odds ratio (OR) for chewing tobacco and risk of developing oral cancer was 4.7 whereas the pooled odds ratio for chewing paan/betel quid with tobacco and risk of oral cancer was 7.1 [90]. Some other causes of oral cancer include smoking, poor oral hygiene, irritation due to ill-fitting dentures, alcohol, rough edges on the teeth and some chronic infections caused by fungi, bacteria or viruses. It is found in middle and older age (50-70 years) but in tobacco users it may be see in younger age (35-40

years). Squamous cell carcinoma can arise from any part of the mucosal lining of oral cavity, pharynx and larynx; however alveolar gingiva, floor of mouth, lip, tongue, hard palate, base of tongue is the most common site [88]. At early stage, it may present red or white patches, nodule, a painless non-healing ulcer, progressive increase in size, sudden tooth mobility, unusual oral bleeding, epistaxis and prolonged hoarseness of voice. In advance stage, it may spread to lymph nodes in neck region or metastasizes to distant sites in the body. In majority of cases it precedes the premalignant condition like leukoplakia, erythroplakia, oral submucous fibrosis and various degrees of oral intra-epithelial dysplasias. Azad et al in their study emphasized that squamous cell carcinoma in tobacco users showed more expression of GLUT-1 which marks the more aggressive nature of the tumor [91]. Diagnosis of suspected lesion is confirmed by biopsy and its histopathological examination.

Types: Gross appearance: cauliflower like **[Figure 15]** (solid outgrowth), ulcero-proliferative, diffuse infiltrative (hard to firm area) Histological: according to tumor cell morphology and arrangement it can be, well differentiated, moderately and poorly differentiated

Prognosis: It is depending on the site, size of tumor, stage of disease and overall health of patient. Treatment of oral cancer involves a multidisciplinary team with specialists from the realms of radiation, surgery, chemotherapy, nutrition, dentistry, and all possibly involved with diagnosis, treatment, rehabilitation, and patient care.

[B] Systemic effects:

Besides nicotine smokeless tobacco and its products contain various harmful substances including tobacco-specific nitrosamines (TSNAs) and toxic metals which enter into systemic circulation and producing various deleterious effects on human health. The metabolites of TSNAs can be detected in urine of smokeless tobacco users and can be used as biomarkers for assessments of a person's exposure to specific TSNAs. Raised TSNAs levels and its metabolites increase the risk for development of various cancer of oral cavity as well as distant organs [6,92].

1. Nicotine Dependence/Addiction: During tobacco chewing its contents mixed saliva when comes with contact of oral mucosa; nicotine and others soluble substances gets absorb and goes to blood circulation. Nicotine present in smokeless tobacco is a potent addictive agent and other substances like flavouring agent and sweetener may further enhance its effects and causing dependence and addiction. Smokeless tobacco consumers feel pleasurable psychoactive effects, but after long term use they continue to crave and use despite of its harmful effects on body. They may sometimes switch to other products with higher nicotine levels and frequently relapse occurs upon cessation. Tobacco users also promote other near ones or friends to tobacco products for enjoyment and celebrations. It has been found that addiction to ST is related to age at initiation, amount and frequency of nicotine ingested per day, and years of use.

Nicotine addiction can lead to an artificially increased heart rate and blood pressure. In addition, it can constrict the blood vessels that are necessary to carry oxygen-rich blood throughout the body. Athletic performance and endurance levels are decreased by this reaction [93].

2. Other organ cancer: Beside the oral cavity and head and neck cancer smokeless tobacco use can cause cancer of other organ of body including esophagus, pancreas, uterine cervix, lung, kidney etc. Studies from Asia, Scandinavia and Sweden shows epidemiologic evidence of a causal association between esophageal, pancreatic, and lung cancer and use of smokeless tobacco including chewing tobacco, snus and snuff [1,6,43,94]. Few researches have detected higher levels of carcinogen (TSNAs) in human cervical cells of smokers than in those of non-smokers [44]. Also studies have confirmed that smoking is an independent risk factor for cervical squamous cell carcinoma. In a case-control study in India showed a significant dose-response relationship between the number of betel quid (paan) with and without tobacco chewed per day and increased risk of invasive cervical cancer [1,40].

3. Reproductive system: various constituents of ST like nicotine, areca nut, PAHs, and several metal including arsenic, cadmium, lead, and mercury in smokeless tobacco products have deleterious effects on reproductive system, causing hormonal irregularity and infertility. They act like developmental toxicants. Metals may cause oxidative stress in cells and interfere with fetal nutrition. Studies suggest that infants born to mother who use tobacco and its products during pregnancy have a higher risk of several adverse outcomes such as pre-term birth and fetal growth retardation.

4. Diabetes and Insulin Resistance: Nicotine in tobacco products increases circulating levels of insulin-antagonistic hormones and impairs insulin sensitivity, hence tobacco users have an increased risk of developing type-2 diabetes [6,96].

5. Cardiovascular system: Nicotine present in tobacco and its product can lead to an artificially increased heart rate and blood pressure. Toxic agents present in tobacco products like nicotine, PAHs, and heavy metals such as cadmium cause damage to the vessels, insulin resistance, hyperinsulinemia, vasoconstriction and inflammation leading to the development of endothelial dysfunction and atherosclerosis. Smokeless tobacco user is associated with an increased risk of ischemic heart disease, hypertension and stroke. Some studies suggest an increased risk of non-fatal cardiovascular disease associated with use of ST including snuff, chewing tobacco, betel quid with tobacco, and mishri/ pan masala.Overall athletic performance and endurance levels are decreased in chronic tobacco/ tobacco product user [97-99].

Others:

Environment and surrounding: Tobacco cultivation and its processing consume lot of water and pesticide which is not eco-friendly. Further small plastic pouches /sachets of packing ma-

terial of ready to use tobacco products thrown by users here and there creates unsightly appearance and also increase burden of plastic garbage, as it is too small to pick-up by rag pickers, and blow away with wind to distant places or water bodies.

Conclusion

It is clear from the various studies from different parts of world, that betel nut alone or with smokeless tobacco and its ready to use products like pan masala and gutkha have significant deleterious effects on dental hard and soft tissues. They are carcinogenic and on chronic use they can cause deadly cancer of oral cavity as well as cancer of pharynx, larynx, esophagus, pancreas, lung, and uterine cervix. It also affects the heart and reproductive system. Thus, there is an urgent need to ban and stop the marketing and advertisement of tobacco and its products as well as areca nut. Legislation against open sale and use of such products should be stricter and more countries should be encouraged to bring out such legislations. Public health programs regarding the harmful effects of smokeless tobacco and betel nuts, along with increased awareness by healthcare professionals of the signs and symptoms of this disease, can inhibit the user from tobacco habit.

These programmes should specially target school going adolescents and young population or they must be taught about side effects to help them to escape from tobacco habit. No street vendor or retail/general shop should be permitted to sell these products as these places are easily approachable to adolescents and school going children. In addition to educating consumers about the health risks of tobacco and betel nut use, we should encourage them to de-addiction. At global level there is needed to reduce tobacco cultivation as it consumes large quantity of water, pesticides and at some places involve child and women labour. Instead, other more useful plants can be cultivated for generation of revenue and this will save money in long term as it reduces cancer burden, cost of medicine and hospitalisation.

Figures

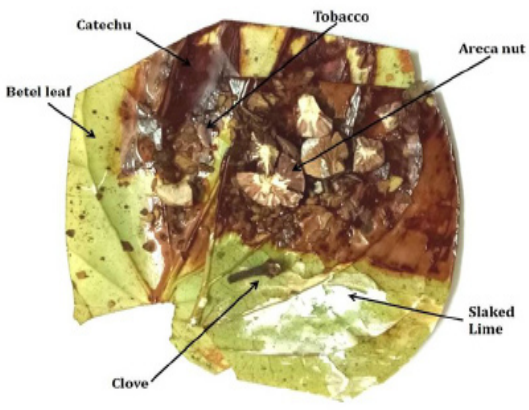

Figure -1: Indian paan with its ingredients.

Figure 1: Indian paan (Betel Quid) decorated with its ingredients

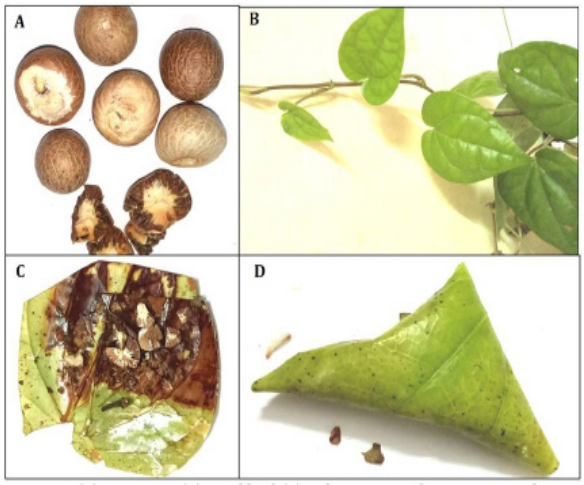

Figure 2: (A) Areca nut, (B) Betel leaf, (C) Indian paan with various ingredients and (D) Folded paan with ingredients ready to chew (Betel Quid)

Figure 3: (A) Gutkha mixed with zarda (tabacco), (B) Gutkha/pan masala Zarda/tobacco, (C) Gutkha/pan masala sachet and (D) Tobacco/zarda in can.

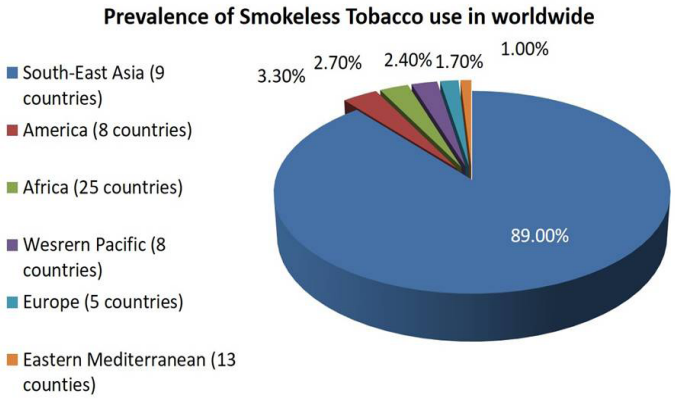

Figure 4: Prevalence of smokeless of tobacco in worldwide.

Figure 4: Prevalence of smokeless tobacco worldwide

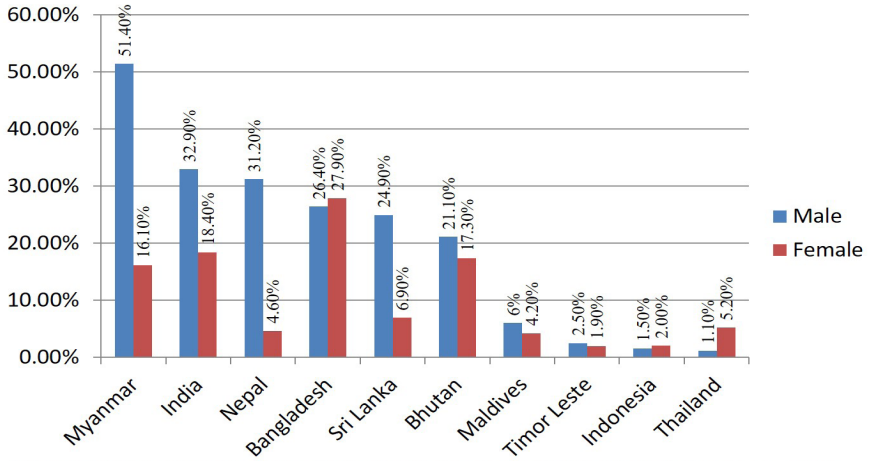

Figure 5: Prevalence of smokeless of tobacco in South-East Asia among male and female. (data source: http://www.searo.who.int/mediacentre/releases/2013/pr1563/en/)

Figure 5: Prevalence of smokeless tobacco in South-East Asia among male and female. (data source:http://www.searo.who.int/mediacentre/releases/2013/pr1563/en/)

Figure 6: Gutkha / Pan masala sachets at street vendor.

Figure 7: Gutkha / Pan masala sachets at retail shop

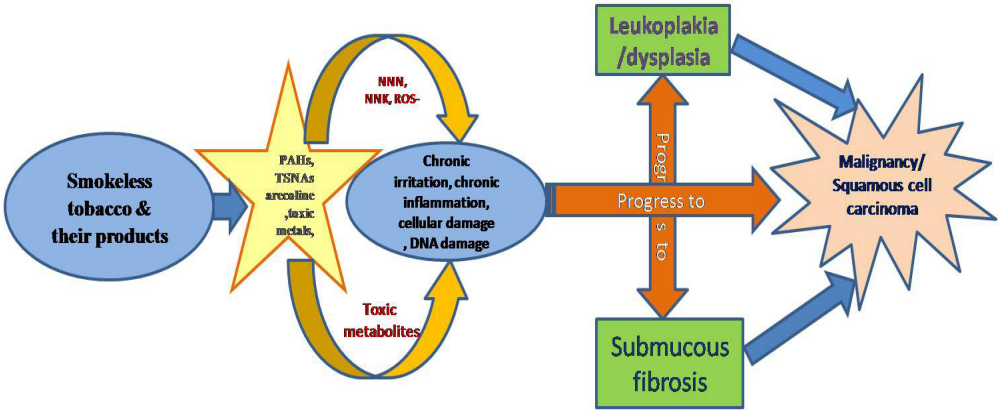

Figure 8: Mechanism implicated in induction of cancer due to use of smokeless tobacco.[TSNAs-tobacco-specific nitrosamines, PAHs-polycyclic aromatic hydrocarbons NNN-(N-nitrosonornicotine)), NNK-methylnitrosaminobutanone, ROS- Reactive oxygen species]

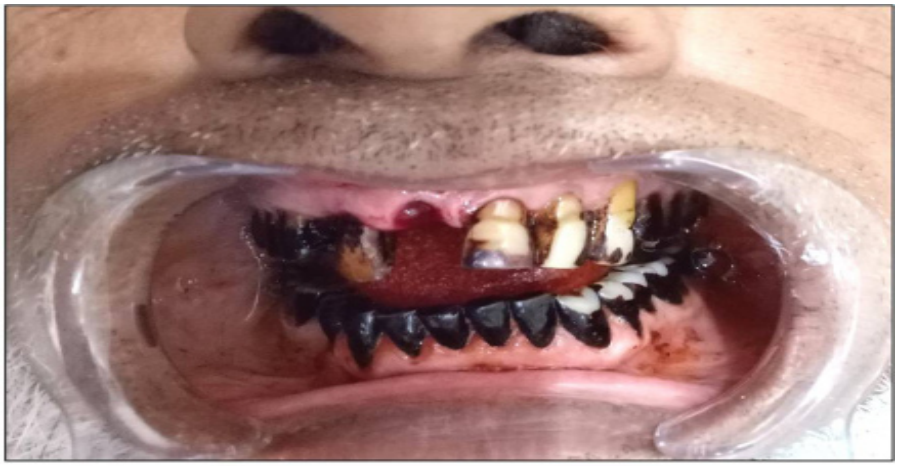

Figure 9: Staining of teeth and fractured front teeth in chronic tobacco chewer.

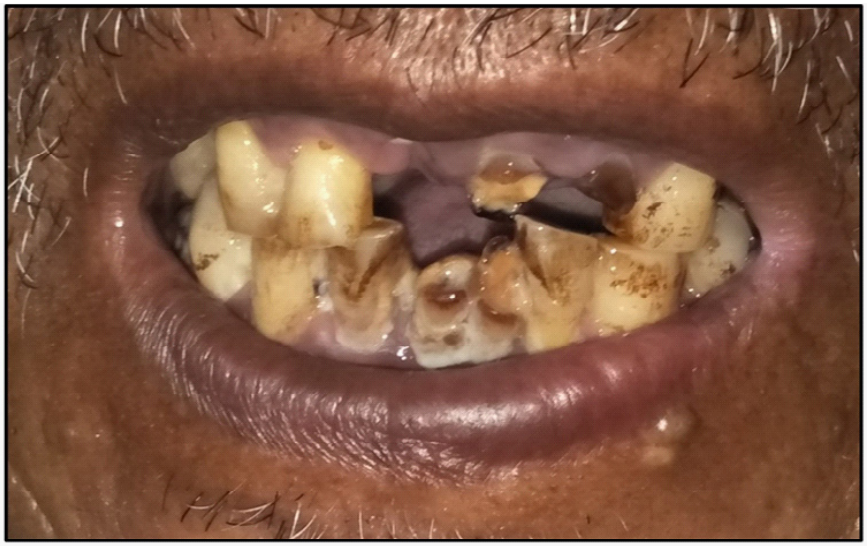

Figure 10: Poor oral hygiene and teeth loss due to chronic tobacco chewing.

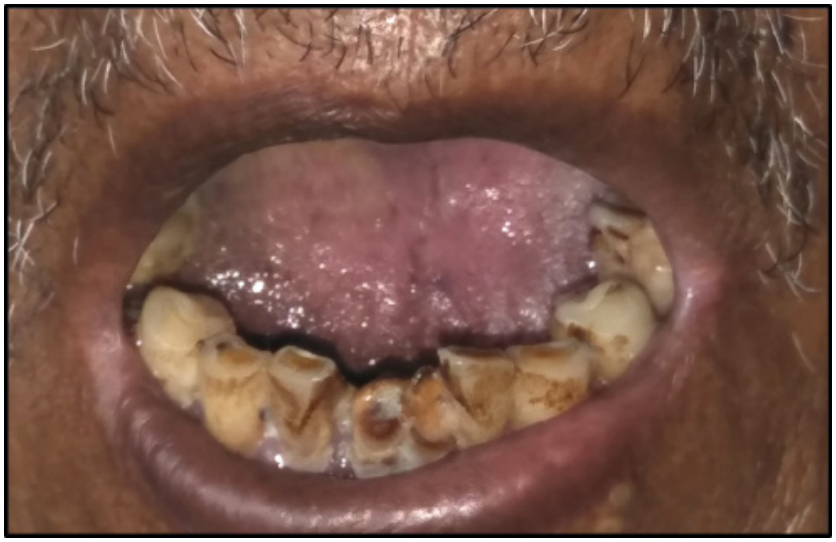

Figure 11: Restricted mouth opening (submucous fibrosis): poor oral hygiene and teeth loss due to chronic tobacco chewing.

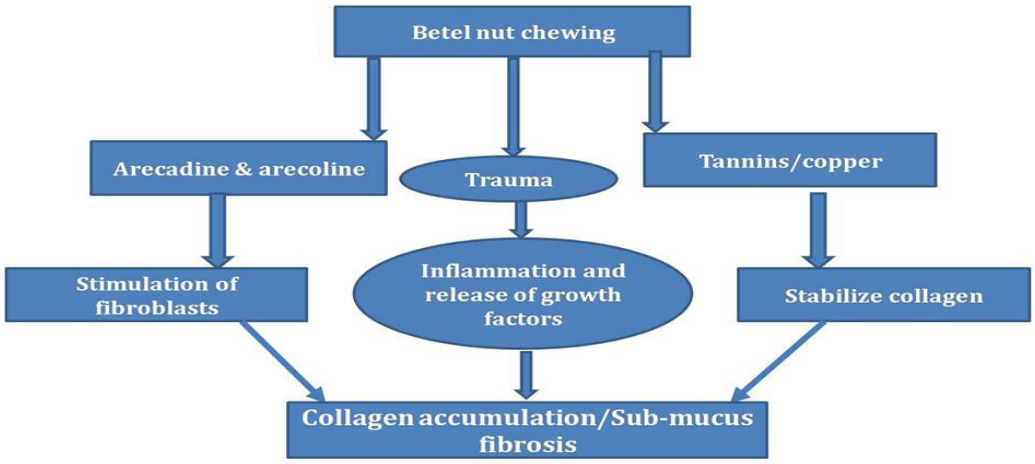

Figure 12: Mechanism of development of sub-mucous fibrosis

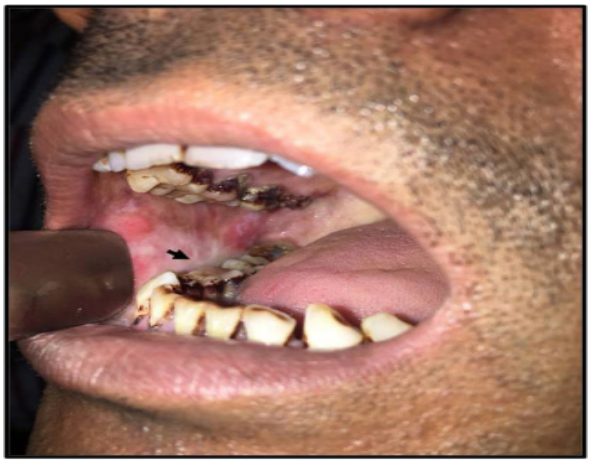

Figure 13: Leukoplakia in chronic tobacco chewer (arrow)

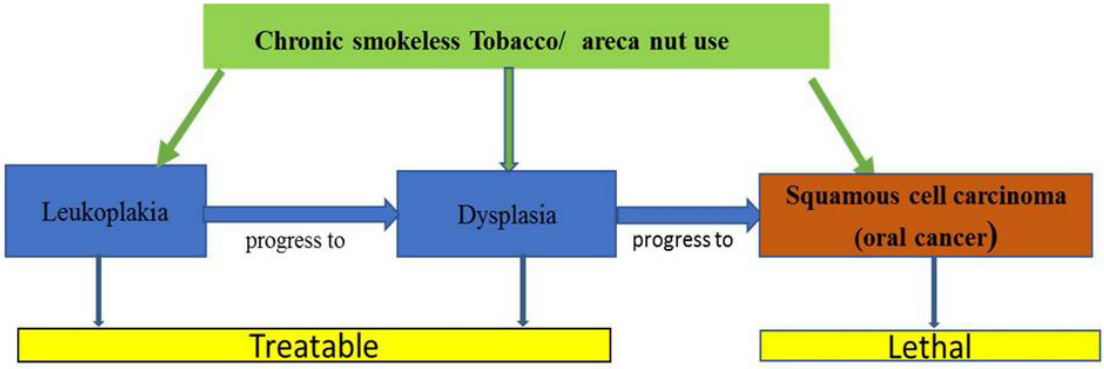

Figure 14: Progression of leukoplakia

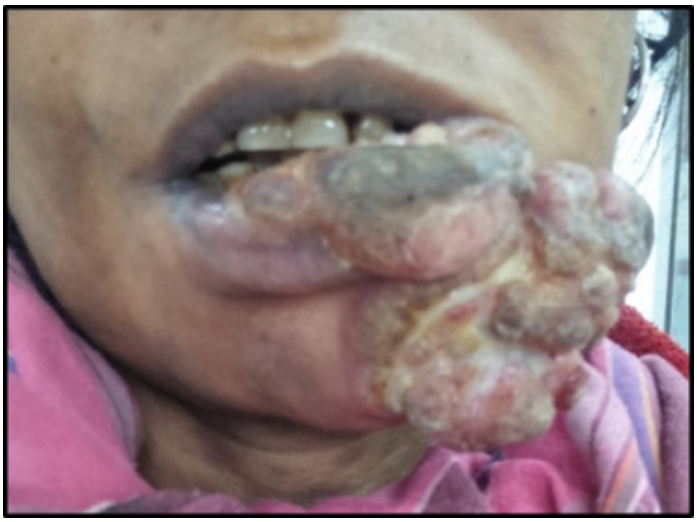

Figure 15: Oral cancer in chronic tobacco chewer.

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