Smokeless Tobacco (*paan and gutkha*) Consumption and its Prevalence Contributing towards Oral Cancer

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ABSTRACT

OBJECTIVES: Smokeless tobacco consumption leads to oral submucous fibrosis (OSMF) condition, which is a long-lasting devastating condition of oral cavity having the potential of malignancy across the world. In this review, we mainly focus on smokeless tobacco such as paan and gutkha consumption, and their role in the induction of OSMF and finally oral cancer.

METHODS: The list of articles to be examined was established using citation discovery tools provided by PubMed, Scopus and Google Scholar.

RESULTS: The continuous chewing of paan and swallowing of gutkha triggers the progressive fibrosis of sub-mucosal mucous tissue. Usually, the condition arises initiated from multifactorial risks especially smokeless tobacco, such as betel quid, areca nuts, and slaked lime used in paan and gutkha, which progressively lead to OSMF. The incidence of oral cancer is high in women as compared to men across the Southern Asian countries. The human oral epithelium cells are affected due to slake lime present in the betel quid and/or with areca nut, which causes carcinogenic and genotoxic effects.

CONCLUSIONS: It is concluded that these products such as 3-(methyl nitrosamino) propionitrile, nitrosamines, and nicotine initiate the production of reactive oxygen species (ROS) present in non-burn tobacco which eventually leads to fibroblast, DNA and RNA damage with carcinogenic effects in the mouth of tobacco consumers. The nitrosamine of tobacco bears metabolic activation by cytochrome P450s may lead to formation of N-nitrosonornicotine (NNK); a major carcinogen and micronuclei (MN); a landmark for genotoxicity, which further leads to DNA damage and finally oral cavity cancer.

Key words: Fibrosis, Oral Submucous, Paan, Gutkha, Betel quid, Areca Nut, Oral cancer
INTRODUCTION

The term smokeless tobacco is used for the consumption of non-burn tobacco, which should be chewed, spit, dip and snuff. People chew the tobacco in the mouth and spit out the juice that builds-up during dipping. Nicotine and other constituents are absorbed in the lining of oral cavity. People of many regions like India, Pakistan, North America and other Asian countries have long history of smokeless tobacco. Approximately, 28 chemical constituents present in the smokeless tobacco are carcinogenic in nature, among which nitrosamine is the prominent one [1].

The people are mostly using paan and gutkha due to lack of awareness and education. They are not aware of the harmful effects associated with their use. However, it has been reported that peoples consuming these products for the beneficial effects like mouth freshener, aid in digestion, germ-killing, astringent, mood enhancers, tension relievers and oral cleaners [1]. Gutkha is sweet in taste and children consider it as a candy. Many people believed that gutkha is a mouth freshener, but its good taste aggregate microbes and spoil teeth. The use of paan and gutkha is difficult to control in most of the countries and its extensive use leads to oral cancer [2]. The consumption of smokeless tobacco and areca nut is high in South Asian countries in the form of “Paan”. In different Asian languages “Paan” simply means leaf. Furthermore, various ingredients are wrapped in the betel leaf. The common components of paan are tobacco, seeds, quenched lime, spices and areca nut enfolded in betel quid [2]. In most of developed and developing countries, the tobacco is widely used with other constituents shown in Table 1. Over three decades ago, India introduced tobacco industry and produced “Gutkha” which consisting of slaked limes, areca nut, chewing tobacco, spices and catechu packed in tins or pouches [2].

**Table 1.** Some common forms of oral smokeless tobacco and its constituents

<table>
<thead>
<tr>
<th>Common/native name</th>
<th>Ingredients</th>
<th>Countries population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toombak</td>
<td>Sodium carbonate and Tobacco</td>
<td>Sudan</td>
</tr>
<tr>
<td>Shammah</td>
<td>Tobacco, slaked lime, and ash</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Naswar</td>
<td>Tobacco, slaked Lime, indigo, cardamom, oil, and menthol</td>
<td>Iran, Afghanistan, Pakistan, Central Asia</td>
</tr>
<tr>
<td>Nass</td>
<td>Tobacco, ash, cotton and sesame oil</td>
<td>Iran, Afghanistan, Pakistan, Central Asia</td>
</tr>
<tr>
<td>Mawa</td>
<td>Areca nut, lime and Tobacco</td>
<td>India</td>
</tr>
<tr>
<td>Gadakhu</td>
<td>Tobacco and molasses</td>
<td>Central India</td>
</tr>
<tr>
<td>Zarda</td>
<td>Boiled tobacco</td>
<td>India and Arab countries</td>
</tr>
<tr>
<td>Paan/betel quid</td>
<td>Areca nut, betel leaf, slaked lime, spice, catechu and with</td>
<td>India Subcontinents, New Guinea, Southeast Asia, and</td>
</tr>
</tbody>
</table>
oral submucous fibrosis (OSMF) Oral cancer is one of the persistent disorders and condition of oral cavity categorized by irritation and progressive fibrosis of superficial and deep connective tissues. Oral cancer has been commonly observed in India, Pakistan, Sri Lanka, Taiwan, China, Indonesia and Malaysia [3, 4]. It is believed that the pathogenesis of OSMF is multifactorial and associated with nutritional deficiency, consumption of smokeless areca nuts, chilies, lime, genetic abnormalities, betel quid, tobacco smoking, Herpes simplex virus (HSV), human papilloma virus (HPV), chronic candidiasis and immunological depression [5]. For instance, the oral cancer was the sixth predominant condition all over the world, involving which involved both genders equally and in developing countries as well, it is was very common among in male individuals [6].

Smokeless tobacco and areca nut consumption in various forms has been part of tradition and culture in United State and South Asia countries. Essentially, areca nut is the fruit, which is derived from areca catechu. It is present in chewable form and also main component in various products daily used in younger population. Areca nut consists of 11-26% of tannin, act a stimulants, and 0.15-0.67% alkaloid mainly arecoline [2].

Areca nuts are extensively used in the present time, which has noxious and stimulant effects. Studies have reported that areca nut leads to diminished hunger, enhanced digestion, altered concentration and relaxation and sometime also increase alertness [2]. The use of gutkha has been shown to have genotoxicity and clastogenic properties [1]. In some condition, alcohol play important role in the oral cancer rather than smoking [7]. The use of smokeless tobacco products with alcoholism and smoking increases the chance of oral cancer. In this study, our main focus is on paan and gutkha consumption, which are common smokeless products and their role in induction of OSMF and ultimately leads to oral cancer.

METHODS

Bibliographic search for the current review was conducted on PubMed, Scopus and Google Scholar for articles on oral cancer due to paan and gutkha consumption. Firstly, “prevalence of smokeless tobacco in Taiwan”, “prevalence in India”, “prevalence in Pakistan”, “occurrence of paan and gutkha in Tanzania”, “presence of smokeless tobacco in Indonesia and Malaysia”, “presence of paan and gutkha in Cambodia” and “prevalence of paan and gutkha in migrated peoples” were used in PubMed search.

The terms included “oral cancer due to paan and gutkha”, “genotoxic effect of paan”, “paan and gutkha chewers”, “betel quid compounds”, “risk factor of oral cancer”, “prevalence of oral cancer”, “paan associated with oral cancer”, “smokeless products lead to oral cancer” and “gutkha usage” were used in Scopus. The keywords such as “carcinogenic effect of betel”, “mechanism of oral cancer due to paan and gutkha”, “Ban of paan and gutkha” and “OSMF mechanism and etiopathogenesis” were used in Google Scholar. The filters data in this article included were related to specially human beings and some laboratory animals. Most studies, which investigated the relation of toxicity of tobacco on the other system, were also excluded.
Furthermore, the articles were excluded if data on oral cancer was associated with other brain and neck cancer. The studies, which focus on single or limited cases having adverse effects without showing a clear role of smokeless tobacco in the pathogenesis, were also excluded. Eventually, a total number of 90 reports indexed in Google Scholar and/or PubMed were found to gratify the criteria of inclusion. Various studies not indexed in PubMed were obtained by manual search in Google Scholar, and 15 such reports which satisfied the criteria for inclusion were further retrieved. Therefore, the total number of studies (n) of included in this review is 105 (Figure 1).
Figure 1. Flow diagram of included studies. The flow chart depicts the number of citation and resources materials that have been screened, excluded and/or included in the review.

GEOGRAPHIC PREVALENCE OF USAGE OF SMOKELESS TOBACCO PRODUCTS AND ORAL CANCER

The chewing habit of areca nut in different products has been reported in many countries such as in Thailand, Sri Lanka, Bangladesh, Pakistan, Malaysia, Cambodia, China, Indonesia and New Guiana. In addition, it is also disseminated in the migrated populations in place like UK, South and East Africa, Australia and North America [4]. The people of New Guiana are using betel quid separately with applied lime kept in the commissure of the mouth [8]. People of Southeast Asian countries, usually use tobacco with betel quid and in addition to that smoking habits are also common among such populations. The societies living in the mountains of the Cambodia, Myanmar, Thailand and Laos add areca with other local plants roots like cinnamon, cloves in the betel quid and consumed [9]. Approximately, 390,000 per annum oral and/or pharyngeal cancers occur in world, which constitute about 58% of South and South-East Asia countries [2]. Some countries consuming smokeless tobacco are discussed below.

Taiwan

Traditionally, tobacco has been consumed as part of culture in some countries of the world. However, in Taiwan an increase in the consumption of paan, gutkha and other smokeless tobacco products have been reported, especially among children and teenagers. Many epidemiological studies reported in Taiwan, where betel leaves or betel inflorescence is used with areca nut. The practice of smokeless tobacco among men and women are 9.8% and 1.6%, respectively [10]. In 1991, a survey based study was done on the residents of Kaohsiung-Taiwan, among 1,162 population individuals of aged 15 years and above were consuming 13.3% betel quid and 2.8% daily chewers [11]. The increase in the usage of betel quid has been investigated in many studies. The phenomenon appears due to the surplus in market and ready-made quid in the shop. More than 53% use of these products started habitually in the family members after grandfather and father [10]. In another school base survey in Taiwan, the consumption of betel quid was high and common among boys than girls. It was also common among students, who consumed alcohol, smoke and had friends, who chewed smokeless tobacco [10, 12]. Betel quid was most primarily observed in professional schools than among senior and junior high school students [12, 13].

India

According to the National Report of Global Adult Tobacco Survey (NRGATS) of India and Bangladesh, the current smokeless tobacco users are 25.9% and 27.2%, respectively. There are 30 different types of products including zarda, which contained dried and boiled tobacco leaves, limes, areca nut, additive, spices and tans [14]. Almost, 30-40% cancer cases reported in India have oral cancer and the most obvious cause is extensive use of tobacco products; either in smoking and/or smokeless chewing products [15]. In addition, these oral cancer occurrence cases
are high due to extraordinary consumption of smokeless tobacco such as *paan* and *gutkha* especially in North India, Uttar Pardesh [16].

In India, the prevalence of oral cancer is high. Moreover, it has been previously documented that besides other factors, the extensive use of *paan*, *gutkha*, and zarda could also contribute in the development of oral cancer [2]. In India, mostly children and teenagers chew *gutkha* occasionally or regularly. In Mumbai, 40% of school students and 70% of college students have been reported to regularly consume *gutkha*. Even, in some states of India, they banned *gutkha* consumption due to its carcinogenic and health hazard effects, but still active black market continue to sell it [2]. In addition, the widespread habit of *paan* and gutkha is not limited to the Indian subcontinents, but it is consumed by immigrants living in United State and Europe [17-20]. In the Indian State of Wardha, the men and women practice of *gutkha* was found to be almost 46.4% and 20%, respectively [18].

**Pakistan**

After India, Pakistan is the second prominent country consuming these smokeless tobacco products. The trend is high in Pakistani males and females, which is 21.3% and 19.3% respectively. More than 90% of oral cancer cases have been reported in different areas using tobacco products, which is a vital factor triggering the oral cancer condition. Study reported that female chewed tobacco more than 10-times a day have high risk of oral cancer in comparison to non-tobacco chewers [21]. Study conducted previously by Muwonge et al., [22] reported that smokeless tobacco users are at high risk of oral cancer along with other abnormalities as compared to with tobacco smokers.

Worldwide, almost 600 million peoples consumed areca nut as tradition and part of routine lifestyle. Many epidemiological studies in India and Pakistan illustrated that almost 3.3-37% people chewed *paan*. In Pakistan and India, oral cancer is the main problem after breast and lung cancer. The top ratio of breast cancer mostly observed among females [23]. The incidence of mouth, tongue, hypo-pharynx, naso-pharynx and lip cancer occurred in Karachi-Pakistan in both male and female equally [16, 24-26].

The uses of these products in different countries are considered as a normal cultural practice. *Paan*, *gutkha*, chaalia, naswar and toombaku are widely used, which ultimately lead to OSMF and oral cancer. Various studies suggested that in Pakistan, India and Nepal, 20-30% prevalence of these products were among adults and teenagers [27-29]. In Karachi-Pakistan, 40% populations have used chewable products of betel, areca and tobacco in their daily life [30]. The overall occurrence of the above products in male and female were 50.3% and 28.5%, respectively. A study conducted in the school children of Karachi-Pakistan, reported that more than 74% of students were addicted to chewable items on daily basis [31]. According to a report in 2006, the general use of *paan*, chaalia, *gutkha*, naswar and tumbaku in different provinces of Pakistan are figured 34.3, 34.7, 46.0 and 50% in Sindh, Punjab, Pathan and Mohajir, respectively [19].

The reliable prevalence of *paan* and *gutkha* is fully documented; though fluctuating results have been described from community investigation. One decade prior study has revealed that 46% of residents of the local public in Karachi-Pakistan consumed *gutkha* habitually on routine basis [32]. Similarly, in another study it has been described that 35% of the patients
visiting a health care center in Karachi-Pakistan, were habitual consumers of paan and gutkha with other tobacco smokeless products [17].

**Tanzania**

In Tanzania, 7% of the native inhabitants are using gutkha on daily basis [33]. Besides, paan and gutkha practice other risk factors, which are mostly involved in the development of oral cancer are shown in Table 2 [21].

![Diagram of Roles of Paan and Gutkha in OSMF](image)

**Figure 2.** Roles of Paan and Gutkha in OSMF [34, 35]

**Cambodia**

In Cambodia, most of the users added tobacco to quid and using, others practice to rub with the gum after chewing betel quid. The consumers of smokeless tobacco were mostly elder women [36]. In epidemiological base study it has been reported that 32.6% of women and 0.8% of men above 15 years of age chewed betel quid. Most of the men were about 50 years of age and women chewers over the age of 39 in this study. In overall, the smoking habit was prevalent in men (43%), but rare in women (4.5%) [37].
In the Pacific island of Palau, areca nut is chewed in green unripe state, with other spices, and flavoring ingredients. Population base study conducted in 1991 revealed that 80% women and 70% men chewed areca nut/betel quid, 80% of whom combined tobacco in their betel quid [38].

**Indonesia and Malaysia**

The use of smokeless tobacco was different in each country like in Indonesia; first betel quid is chewed and finally a gob cut tobacco is used to clean the teeth, while keeping in mouth for a moment [8]. In Malaysia, *paan* and *gutkha* is highest among some of the indigenous groups, who also add betel quid to the tobacco.

**Table 2. Summary of risk factors for oral cancer available from various Asian Countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Associated risk factors</th>
<th>Study Design</th>
<th>Number of Subjects in the studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>Quid without tobacco, Smoking, Alcohol, Heavy metals, HPV, Socioeconomic conditions (SEC)</td>
<td>Questionnaire based</td>
<td>4906</td>
<td>[12]</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Quid with tobacco</td>
<td>Visitors to cancer centers and institute of odontology, relevant publications in Vietnamese, interviews with betel quid vendors and individual betel quid</td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Pakistan</td>
<td><em>Paan</em>, <em>Gutkha</em></td>
<td>Structured</td>
<td>425</td>
<td>[19]</td>
</tr>
<tr>
<td>Country</td>
<td>Study Design &amp; Study Variables</td>
<td>Sample Size</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Betel quid, tobacco, Cross-sectional community-based study</td>
<td>1029</td>
<td>[40]</td>
<td></td>
</tr>
<tr>
<td>Yemen</td>
<td>Cigarette smoking, Smokeless tobacco, Quid with tobacco, History based study</td>
<td>649</td>
<td>[41]</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Quid with or without tobacco, Smokeless tobacco, Alcohol, Bidi and cigarette smoking, HPV, Diet, SEC, Nested case-control design</td>
<td>1692</td>
<td>[22]</td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>Quid, Smoking, Case-control study</td>
<td>566</td>
<td>[42]</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Family history of cancer, Alcohol, Smoking, Quid with tobacco, Case-control study</td>
<td>104</td>
<td>[43]</td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td>Malnutrition, HPV Research analysis of frozen samples of oral tissue</td>
<td>210</td>
<td>[44]</td>
<td></td>
</tr>
<tr>
<td>Nepal</td>
<td>Bidi, Epidemiological study, Population aged more than 15 years</td>
<td></td>
<td>[45]</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>Malnutrition, Alcohol, Cigarette smoking, SEC, Case-control study</td>
<td>140</td>
<td>[46]</td>
<td></td>
</tr>
</tbody>
</table>
Usage in migrated communities

The high risk of oral cancer in the migrated people in the UK is due to massive consumption of betel quid and other smokeless products. The people, who migrated from Pakistan, India, Bangladesh and Sri Lanka to UK, are the major betel quid intake communities [47]. Various studies results illustrated that over 80% of adults of Bangladesh in London used betel quid and other products with no gender differences. The use of tobacco in smoking form or in other smokeless form is common among men and women [48, 49]. The usage of these industrial products is also becoming famous among these migrated communities. Studies done on betel quid and tobacco practice among emigrant individuals of South Asians in Western also point out the lack of awareness leading to oral cancer regardless to gender, age, national group and social class. They tend to be more aware of smoking, but not attentive of other oral cancer habits like paan and gutkha consumption responsible to initiates.

MECHANISM OF GENOTOXICITY AND CARCINOGENICITY

These paan, gutkha and zarda are taken by mouth, chewed, sucked, or applied among teeth and gums. World Health Organization (WHO) has classified smokeless tobacco products as human carcinogenic compounds, in particular tobacco-specific nitrosamines (TSNA), which account for 76-91% of the total N-nitroso compound (NOCs) burden [14]. These products have been associated with oral and pancreatic cancers, cardiovascular disease, periodontal disease, asthma and deformities in reproductive system of women [1]. The mechanism of paan and gutkha developed in human are summarized in Figure 2. Different studies have shown that tobacco users with slaked lime in betel quid or with areca nut cause carcinogenic and genotoxic affects the human oral epithelium cells. These products generate reactive oxygen species (ROS) in the oral cavity of chewers [50]. The study conducted in India has reported that highest DNA disruption was observed in the gutkha consumers along with smoking lifestyles. While decrease in the DNA denaturation was observed in the following order: Gutkha + smoking > Paan + smokers > Gutkha chewers >Paan chewers > smokers > nonsmoker [51].

The different ingredients used in paan and gutkha have their own detrimental effects such as catechu consisting of tannin and polyphenols, which have high affinity towards esophageal cancer, mutagenicity and clastogenicity [52-54]. Lime used can lead to formation of alkaline pH and this condition developed by calcium hydroxide in slaked lime, which ultimately trigger ROS cause irritation of oral mucosa and hyperplasia [55]. Areca nut consists of phenolic compounds and tobacco releases various nitrosamines in the mouth responsible for proliferative abrasions, DNA and fibroblast damage [34, 56].

A Mexican study in 2006 indicated that the single-cell gel electrophoresis (SCGE) is a safe method to determine DNA damage in human population [57]. When the amount of ROS production in cells enhanced from the competency of normal detoxification system then oxidative stress leads to cellular damage, along with DNA damage [58]. This DNA destruction may occur in double strand (ds) or single strand (ss) DNA breaks [59]. Areca nut is the main component of paan and gutkha, while the areca nut used in gutkha leads to OSMF [60]. The incidence of micronucleus (MN) was originated among OSMF patients chewing gutkha [51]. The studies have shown that ROS production lead to triggered OSMF [61]. The extraction of
NOCs related to areca nuts, which contain active substance 3- (methyl nitrosamino) propionitrile, cause genotoxicity and cytotoxicity responsible for tumors in buccal cavity of smokeless tobacco consumers [62]. The high duration and frequency of paan and gutkha in mouth gums lead to inflammation of oral mucosa, which causes the activation of T-cells and macrophages, ultimately elaborate chemical substance like prostaglandins (PGs). PGs production occurred from keratinocytes of buccal cavity due to areca nut extract, which play significant role in oral tissue fibrosis and cancer. Cytokines like interferon-α, tumor necrosis factor (TNF), interleukin-6 (IL-6) and growth factor like transforming growth factor-beta (TGF-β) were produced at irritation site [63]. These chemical substances are important for the OSMF and premalignant condition (Figure 3).

![Figure 3. Initial event of disorder Mouth Cancer [56, 63]](image)

Genotoxic effects occurred from paan and gutkha mostly due to the presence of nitrosamine shown in Table 3. The nitrosamine in the chewers’ saliva undergoes nitration during betel quid, when it reacts with nitrite in the presence of catalyst [34, 64]. This nitrosamine of tobacco endures metabolic activation by cytochrome P450s may lead to formation of N-nitrosonornicotine (NNK), a major carcinogen [65], which further leads to DNA damage and finally oral cavity cancer. MN is small chromatin bodies that appear during cell division in the cytoplasm due to condensation of whole chromosome or acrocentric chromosome which was the
only biomarker used to identify genotoxicity during sister chromatid exchange (SCE) and chromosomal aberrations (CA) [66]. Multiple genes are involved in the breakdown of carcinogens, and the most often observed evidences have been explored that cytochrome polymorphism (CYPs) affect the risk of oral cancer. Arecaidine, arecoline and other similar ingredients of betel quid exists in minute quantity in human blood and arecoline quantity was also associated with the use of betel quid [67]. We have summarized the effects of CYPs, which are connected with chewing of betel quid and lead to the cancer of oral cavity and pharynx in Figure 4. Among the CYPs; the CYP1A1 and CYP2E1 may trigger the nitrosamines, which ultimately effects mouth potentially leading toward malignant disorders [68]. While μ-glutathione-s-transferase (GST-μ), TNF-α were also enhanced. Meanwhile, from few decades the MN is used as a biomarker for the evidence of genotoxic effects. The prolong use of chewing or masticatory products like supari, paan and gutkha can lead to the development of different types of oral cancer. So, it is necessary to evaluate the population at high risk those who are mostly using these products in high portion on daily bases. Paan and gutkha have been found to have carcinogenic effects in laboratory animals causing tumors in different organs like in liver, mouth, pharynx and larynx. Paan act as cancer promoter agent in the mouse [69]. A study was conducted in which mice were fed with paan or gutkha in the feed lead to generation of tumors in different organs like tastes, ovary, liver, kidney, stomach and lung. Which has been revealed that gutkha and paan both are carcinogenic not only for oral cavity, but may also lead to deleterious effects in other organs as well [70].

![Figure 4. Molecular mechanism of gutkha](image-url)
DISCUSSION

Studies have shown that paan and gutkha contain other trace elements like magnesium, chlorine, calcium, sodium, manganese, copper, bromine and vanadium. The copper contents in these two products were much more in concentration instead of other nuts consumed by human being. The average content of copper in these processed products available in betel nuts was 18±9 µg/g, which leads to deleterious effects on human health. According to Indian Food Report, this concentration was 2.5 times greater than the raw betel nut. The cellular metabolism of betel nuts and quid leads to production of ROS, such as hydrogen peroxide and superoxide anion radicals at pH more than 9.5 [35]. The saliva has the potential to inhibit the production of these ROS and other free radicals from betel quid and nuts constituents. But still H₂O₂ and O₂⁻ production occur due to alkaline pH, which comes from the addition of slaked slime during chewing used in these products [71, 72].

Table 3. Studies that indicates genotoxicity of paan and gutkha

<table>
<thead>
<tr>
<th>S. No</th>
<th>Study</th>
<th>Source</th>
<th>End points</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Paan/gutkha</td>
<td>BC</td>
<td>MN</td>
<td>[73]</td>
</tr>
<tr>
<td>2.</td>
<td>Tobacco</td>
<td>EOMC</td>
<td>MN</td>
<td>[74]</td>
</tr>
<tr>
<td>3.</td>
<td>Betel quid, areca</td>
<td>BC and PBL</td>
<td>CA and MN</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>and tobacco</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4.</td>
<td>Tobacco</td>
<td>EBC and PBL</td>
<td>MN and CA</td>
<td>[76]</td>
</tr>
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<td>5.</td>
<td>Paan</td>
<td>CC</td>
<td>CA, SCE and MN</td>
<td>[77]</td>
</tr>
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<td>6.</td>
<td>Paan/Betel quid</td>
<td>TRP</td>
<td>QBT</td>
<td>[78]</td>
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<td>7.</td>
<td>Lime</td>
<td>EOMC</td>
<td>CT and MN</td>
<td>[71]</td>
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<td>8.</td>
<td>Slaked Lime</td>
<td>PMB</td>
<td>HE</td>
<td>[79]</td>
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<td>STS</td>
<td>Mutagenicity</td>
<td>[80]</td>
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<td>HBEC</td>
<td>CFFA, NRA, TRA</td>
<td>[81]</td>
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<tr>
<td>11.</td>
<td>Paan</td>
<td>Ovary cells</td>
<td>SCE and CA</td>
<td>[82]</td>
</tr>
<tr>
<td>12.</td>
<td>Tobacco Products</td>
<td>ME, CTLE</td>
<td>Ames assay</td>
<td>[83]</td>
</tr>
<tr>
<td>13.</td>
<td>Catechu</td>
<td>Liver tissue</td>
<td>Ames assay</td>
<td>[84]</td>
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<td>14.</td>
<td>Arecoline</td>
<td>BMC</td>
<td>SCE</td>
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<td>15.</td>
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<td>16.</td>
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<td>SCE, CA and MN</td>
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<td>17.</td>
<td>Paan, Tobacco</td>
<td>HOK</td>
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<td>18.</td>
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<td>19.</td>
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<td>20.</td>
<td>Paan</td>
<td>Mice</td>
<td>MA</td>
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<td>21.</td>
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<td>TRP</td>
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<tr>
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<td>SNT</td>
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List of abbreviations


It seems that there is an association between oral inflammatory conditions and age of individual using smokeless tobacco products [95]. However, *paan* and *gutkha* may also expose the consumers to other oral mucosal disorders at any stage of life. Javed et al., [32] illustrated that populations at the age of 45-65 years have more periodontal inflammation in *gutkha* chewers. A study that investigated the effects of smokeless tobacco on blood flow responses has been shown that tobacco significantly increases the gingival blood flow, arterial blood pressure and heart rate [96]. In addition, the *paan* and *gutkha* chewers also declined salivation and mucous formation, thereby reducing the normal micro-flora of oral cavity and exposing mouth to pathogens like *aspergillus* species [97]. And that’s why by dropping salivation in mouth may also permit pathogens to deteriorate in the supra and sub-gingival area, thus persuading periodontal inflammation in *gutkha* chewers compared to non-chewers [98].

OSMF was an infrequent disease/condition during 1960s and 1970s, prominent in older individuals approximately 0.1-0.5%. Later on in India subcontinents consumption of areca nuts mixtures in different products like in *paan* and *gutkha* has placed an epidemic OSMF in adolescents [99, 100]. Various case control studies in New Delhi, Maharashtra, Gujarat, Nagpur and Bhavnagar suggested that more than 70% cases of OSMF occurred in people below 35 years of age [99-101]. *Paan* and *gutkha* chewers develop the condition frequently as compared with betel quid chewers. The incidence of OSMF is 75% in 4.5 and 9.5 years due to *paan* and betel quid, respectively. The lack of betel quid leaf in *paan* and higher levels of areca nuts may be the possible ingredient to develop OSMF in *paan, gutkha* users [102].
Areca nuts mixed with tobacco is not an etiological agent to develop sub-mucous fibrosis. However, it is thought that high occurrence of OSMF take place due to its effect of enhancing addiction and thus initiating higher exposure to areca nuts chewing. In different studies, OSMF was recognized as an extremely precancerous state. In a cohort study, 12,212 tobacco consumers were at relative high risk of malignant transformation in OSMF compared to tobacco users without any precancerous lesions [103]. There were enough indications that betel quid with tobacco, chewing of tobacco with lime and/or betel quid without tobacco and areca nut are human carcinogen [104]. The use of these products reached to such proportion that government has no choice to ban these products. In public health, banning of such extensively used products is difficult and not ideal. Especially, the betel quid essentials should be banned, as paan and gutkha used as a food item containing betel quid. Although, central committee of food safety of India issued letters to Central Government to ban betel quid, areca nut, paan and gutkha.

The reasons due to which central committee of food safety consistently want to ban manufacturing and marketing include; a). Adolescents and teenagers are getting more addicted, b). Consumers develop OSMF, precancerous condition and cancer in shorter duration compared to smokers and c). Females preferred smokeless tobacco more due to social disapproval of smoking and finally addicted to gutkha. So in India, all legal evaluation processes for banning gutkha nationally have been accomplished. But still its manufacturing and marketing is going on in black or legally.

In the following States of India gutkha and paan have been banned: Andhra Pradesh; Goa; Maharashtra 01 August 2002, Tamil Nadu, 19 November 2001. Certainly, gutkha producers have disappeared on the defensive [105]. Later on gutkha and paan producers stated that these are not bad, as these products were stay free by UK and Singapore according to Time of India News. So, they are exporting paan and gutkha to UK, Singapore, Middle East, Japan and Australia as well as across South Asia.

CONCLUSION AND RECOMMENDATION

From the present study, it is concluded that extensive use of smokeless tobacco in different forms leads to OSMF, which potentially transform to malignant condition in all age population. The genotoxic and carcinogenic effects of smokeless tobacco initiated in the oral cavity due production of ROS and free radical. These free radicals and ROS productions damage the normal DNA and RNA, which leads to genotoxicity and eventually oral cancer. As previously described mechanism explain the induction, maintenance and progression of OSMF due to paan and gutkha. Strict cessation, follow-up and termination of smokeless tobacco should be followed to reduce the incidence of oral cancer. Widespread use of these spices and other products in children, as well as in adolescents mostly practice due to taste and low cost followed by easy availability. In this new era, the oral cancer is increasing day by day due to use of these smokeless tobacco products in particular the lower socio-economic levels that constitute the large majority. So it is important to establish data management, monitoring, and evaluation system. In addition, oral cancer control policies should be taken into account to change the lifestyle and behavior of the high risk population.

CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.
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ETHICAL APPROVAL

Not required.

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