

## Genotoxic and Carcinogenic Effect of Gutkha: A Fast-growing Smokeless Tobacco

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### Review Article

#### Abstract

Oral cancer is a highly lethal disease and one of the most debilitating and disfiguring of all malignancies in the world. According to Global Adult Tobacco Survey (GATS) 2010 report, 60% of tobacco users in India use only smokeless tobacco. Among 206 million smokeless tobacco users, 65.1 million are consuming gutkha. In recent years, gutkha is recognized as a life threatening disorder with the serious health consequences. The aim of this review is to increase the attention to complete ban of tobacco use, awareness, knowledge, and beliefs of public about the harms of not only gutkha but also all other tobacco products and also to promote the intentions to quit the habits.

**Keywords:** Tobacco; Gutkha; Oral cancer; Carcinogens

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## Introduction

Tobacco use is a main cause of oral cancer and a preventable cause of premature death in India.<sup>1,2</sup> According to Global Adult Tobacco Survey (GATS) 2010 report, the majority of 60% Indian tobacco users use only smokeless tobacco.<sup>3</sup> In recent years, a combination of areca nut and tobacco has been introduced in India known as gutkha (chewable tobacco form). Gutkha is consumed in most parts of India as a mouth freshener.<sup>4-8</sup>

## Epidemiology

In India, there are 275 million tobacco users, constituting 35% of adults (as per GATS survey). This figure is made up of 164 million smokeless tobacco users, 69 million smokers, and 42 million people using both smoking and smokeless forms of tobacco.<sup>9,10</sup>

In India, 53.9 million men and 11.1 million women, 48.6 million of rural population and 16.5 million of urban population consume gutkha.<sup>11</sup>

The dependency on tobacco and damage of health due to gutkha consumption is recognized as a life threatening disorder with the health consequences.<sup>12</sup> The increased use of gutkha has led to the highest incidence of oral cancer in India.<sup>13</sup> If the present consumption rate of tobacco continues, it has been estimated that by mid 21st century there could be one billion premature deaths globally.<sup>14</sup> Tobacco is directly linked to general health and economy of the entire world. This review is more concerned about tobacco consumption and its direct and indirect effects on society.

## What is gutkha?

In 1975, the areca nut industries, using traditional Indian technology, along with the tobacco industry developed a dry preparation.<sup>15</sup> This product without tobacco is known as 'Pan masala', while the product with tobacco is known as 'Gutkha'.<sup>16</sup>

Commercially manufactured gutkha consists of sun-dried, roasted, finely chopped tobacco, areca nut, slaked lime, and catechu. This blend is mixed together with several other ingredients such as flavorings and sweeteners.<sup>17,18</sup> It is either held in the mouth, sucked, or chewed. Saliva is generally spat out, but sometimes swallowed. Now, gutkha use has spread gradually to all parts

of the world like South Asia, Europe, Canada, United Kingdom, and United States of America largely by South-east Asian expatriates.<sup>11,19-22</sup>

## Why has gutkha consumption increased?

Gutkha has made inroads in traditional society and people with lower socioeconomic status as an alternative source of smoking.<sup>23</sup> The myth in favor of gutkha that it is less harmful than smoking products is a major challenge in India.<sup>14</sup> Gutkha consumption has increased because of aggressive advertisement, and convenient packed sachets, which is available in various brand names in almost all shops at affordable cost.<sup>24</sup> The widespread marketing of gutkha with strategic placement of kiosks near schools has led to a widespread addiction amongst school-going children as well.<sup>25</sup> Gutkha use can begin from early age of childhood due to its flavored sweet taste, easy availability, cost effectiveness, and instant stimulus. Gutkha's ease of procurement and storage, and also lack of social stigma may promote the switch from paan or smoking to gutkha.<sup>26</sup> Many people use gutkha to obtain the psychoactive effects of nicotine. Some authors reported that all users thought that tobacco use may enhance the sense of wellbeing, reduce anxiety and appetite (in taxi drivers), produce arousal or relaxation, relieve tension, help concentration (in clerks, cashiers), combat bad breath, and also may be considered as a leisure activity.<sup>27,28</sup> Some researchers found that habit of gutkha chewing is very difficult to quit.<sup>29</sup>

## What does gutkha contain?

Nearly 4200 chemical constituents have been identified in gutkha.<sup>30</sup> The main carcinogens in gutkha are derived from its ingredients including tobacco, areca nut,<sup>31</sup> lime, and catechu. Gutkha (pan masala with tobacco) has been proved to be a carcinogenic agent<sup>32</sup> (Table 1).

## 1. Tobacco

*Tobacco specific nitrosamines (TSNAs):* Carcinogenic TSNAs in various tobacco products are responsible for numerous cancers. Gutkha products have four TSNAs, namely (i) N<sup>1</sup>-nitrosonornicotine (NNN), (ii) N<sup>1</sup>-nitrosoanatabine (NAT), (iii) N<sup>1</sup>-nitrosoanabasine, and (iv) 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).<sup>33</sup>

**Table 1.** Ingredients of gutkha

Ingredients	Constituents	Origin/preparation	Carcinogens/products
Areca nut	Polyphenols: Flavonoids, Tannins Alkaloids: Arecoline, Arecaidine, Guvacine, Guvacoline Carbohydrate, Fat, Proteins, Crude fibers, Minerals	Unripe/ripe, whole/sliced raw/roasted/sundried boiled/soaked in water fermented (under mud)	Arecoline, MNPN
Tobacco	Aliphatic/aromatic hydrocarbons, Alkaloids- Nicotine, Nornicotine, Cotinine, Anatabine, Anabasine	Sundried, fermented boiled with molasses perfumed concentrated extract (Kiwam)	NNN, NNK, NAT, NAB,* Benzo (a) Pyrene (BaP), toxic metals
Catechu	Catechu- Tannic acid, Acacatechin, Quercetin, and Catechu red	Extracted form heartwood of Acacia Catechu or Suma leaves of Uncaria Gambler, bark of Lithocarpus Polystachya (nang ko)	ROS when used with lime
Slaked lime	Calcium carbonate	From coral, shell fish, quarried lime stone	ROS when used with lime
Spices	Clove, cardamom, aniseed	Plants	-
Sweeteners	Sugar, saccharine	Sugar cane	-
Essences	Menthol, mint, saffron, sandalwood, and musk ketones.	Plants, trees	-

\*Tobacco specific N-Nitrosamines

MNPN: 3-(methylnitrosamino) propionitrile; ROS: Reactive oxygen species; NNN: N'-nitrosomnicotine; NAB: N'-nitrosoanabasine; NAT: N'-nitrosoanatabine; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

The presence of nicotine is the main reason of addiction and resultant maintenance of chronic gutkha consumption habit.<sup>34</sup>

Metabolically activated TSNAs induce mutations in susceptible genes by forming DNA adducts, leading to tumor initiation. Tumor growth is promoted by binding of nicotinic acetylcholine receptors and TSNAs leading to deregulated cell proliferation which increases the survival and metastasis.<sup>35</sup>

## 2. Areca nut

**Areca nut-specific nitrosamines (ASNAs) :** Areca nut is the most abundant ingredient of gutkha, composed of tannins, alkaloids, free fatty acids, polysaccharides, fibers, and minerals like copper. Among the chemical constituents of areca nut, alkaloids are the most important biological carcinogens. The nut contains alkaloids like arecoline, arecaidine, guvaccine, and guvacoline.<sup>36</sup>

(A) Alkaloids: Alkaloids are chemically reduced pyridines. Areca nut contains primarily two biologically relevant alkaloids: arecoline and arecaidine. The most common alkaloid of areca nut is arecoline (1,2,4,5-tetrahydro-1-methylpyridinecarboxylic acid; molecular weight 155.19 Da) followed by arecaidine (1,2,5,6-tetrahydro-1-methyl-3-pyridinecarboxylic acid; molecular weight 141.17 Da). Some other alkaloids are also

present in minor amounts in areca nut such as guvaccine, guvacoline, and arecolinidine.<sup>11</sup> Arecaidine stimulates collagen synthesis and proliferation in a dose-dependent manner and higher concentrations being cytotoxic.<sup>37</sup> Arecoline and arecaidine synthesize greater concentration of collagen to promote submucous fibrosis.<sup>38</sup>

(B) Polyphenols: Two major polyphenols of areca nut include catechin and flavonoids. During chewing of gutkha, oxidation of polyphenols stains the oral soft tissue and hard tissue in typical red color. They stabilize collagen fibers and retard their degradation process.<sup>37,39</sup>

(C) Tannins: Tannins are polyphenols that are capable of precipitating collagen proteins. The outer portion of the areca nut predominantly contains gallotannic acid that cause cross linking of collagen fibers and making them resistant to collagenase enzyme.<sup>37,39</sup>

## 3. Slaked lime

The lime powder is used to enhance the stimulant effect of the betel nut. This occurs as it hydrolyses the arecoline from the nut to produce the central nervous stimulant.<sup>40</sup> The calcium hydroxide content of lime leads to alkaline conditions in the oral cavity with the presence of areca nut which is a major factor responsible for the formation of reactive oxygen species (ROS). ROS causes

oxidative damage in the DNA of cells.<sup>41</sup> Lime is also known to cause irritation and hyperplasia of the oral mucosa.<sup>37</sup>

#### 4. Catechu

Catechu is a reddish-brown substance used in gutkha as an astringent.<sup>11</sup> Tannin and polyphenols are the main constituents of catechu. Catechu combined with lime at an alkaline pH is the most potent producer of ROS.<sup>37,42</sup> Catechu has mutagenic and clastogenic activity.<sup>11</sup>

#### 5. Flavoring agents

Musk ambrette and musk xylene are well known synthetic flavouring agents used in gutkha preparations. Their presence has been detected in the saliva of chewers of betel quid with tobacco. Of the two agents, musk ambrette was found to be mutagenic in Salmonella typhimurium TA100,

in comparison to musk xylene which lacked mutagenicity in Salmonella/microsome test.<sup>42,43</sup>

#### 6. Others

A wide range of toxic metals including mercury, lead, cadmium, chromium, zinc, arsenic, nickel, and high percentage of copper and other trace elements have been found in Indian tobacco product, gutkha.<sup>2,44</sup> The copper content in raw and processed areca nut is higher than other nuts.<sup>11</sup>

Mechanism of gutkha carcinogenicity (Figure 1)

#### Physical trauma

Gutkha contains a large amount of areca nut which has abrasive nature causing repeated mechanical trauma to the oral mucosa.<sup>45,46</sup> Because of the fine particle size of gutkha, there is a high probability of particle adhesion to physically abraded mucosa.<sup>37</sup>

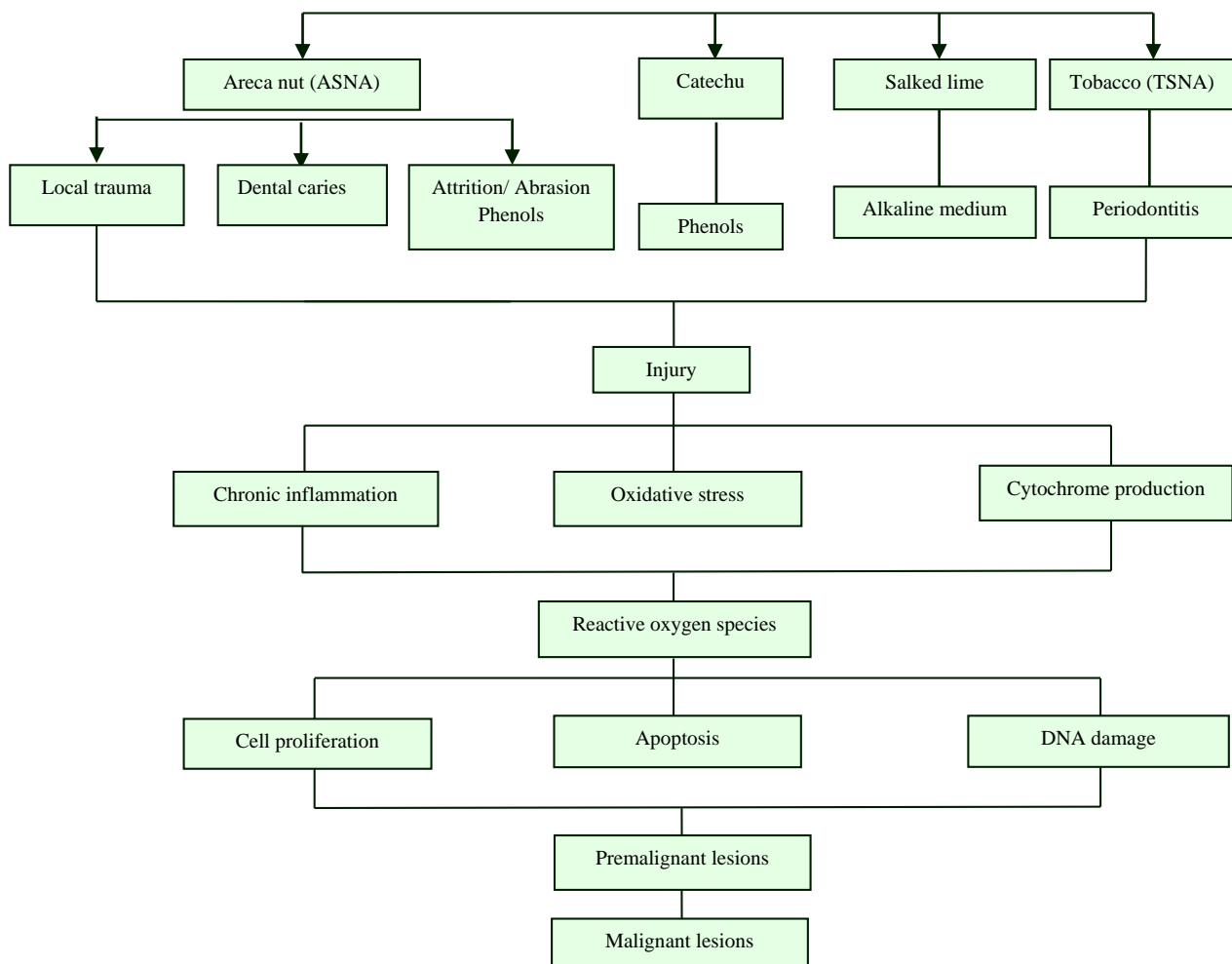


Figure 1. Mechanism of carcinogenicity in gutkha and pan masala (pan masala + tobacco)

## Inflammation

Inflammation is now regarded as an important hallmark of cancer.<sup>47</sup> Chronic use of gutkha causes oral mucous membrane damage leading to inflammation and increased ROS and cytokine levels.<sup>48</sup>

## Genotoxicity and carcinogenesis

TSNAs in the saliva of chewers are derived from tobacco. Areca nut and catechu are capable of generating superoxide anion and hydrogen peroxide at pH > 9.5.<sup>37</sup> During this procedure, ROS concentration increases as soon as the areca nut and catechu polyphenols mix together in presence of slaked lime in the saliva of gutkha chewers. The formation of high level of ROS close to the traumatized oral mucosa can cause direct damage to the tissue.<sup>19,37</sup>

ROS and oxidative stress induce cell proliferation and apoptosis. Chronic use of gutkha induce oral potentially malignant disorders and subsequent malignancy.<sup>37</sup>

The genotoxic effects are most likely caused by the combination of tobacco and ASNAs in gutkha.<sup>42</sup> TSNAs are procarcinogens that ultimately convert into carcinogens. DNA bases have some nucleophilic sites that react with metabolites. Some studies stated that microsomal cytochrome P450 (CYP) system activates<sup>49</sup> tobacco mutagens like polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, and benzene. Metabolism of carcinogens converts

them into harmful reactive species which leads to DNA damage.<sup>50,51</sup>

DNA repair mechanism maintains the DNA integrity and prevents cancer development. These smokeless products are affecting the DNA repair pathway leading to genotoxicity and eventually cell death.<sup>52</sup>

The quantity of ROS can cause cellular damage as well as DNA damage.<sup>52,53</sup> The TSNAs can cause DNA mutation and by altering the protein function may cause oral carcinogenesis.<sup>37,52,54</sup>

## Why should gutkha be banned?

Gutkha mainly is used by men under the age of 50 years.<sup>6,45,55-57</sup> It also is used by women including pregnant ones.<sup>58-61</sup> Nowadays, use of gutkha has increased very rapidly in minors as well.<sup>8,25,62</sup> It is highly addictive comparing to other tobacco products.<sup>63</sup> It contains high carcinogenic products like areca nut and tobacco.<sup>11,19,64</sup> Roughly, 5 million children under the age of 15 have been estimated to be gutkha addicts.<sup>65,66</sup> Some persons spit in public places like hospitals, schools, bus stands, railway stations, etc., and make them dirty. These unhygienic areas provide the favorable environment for bacterial and viral growth.

## How gutkha affects the health?

The use of smokeless tobacco has oral health consequences and it may also affect other parts of the body. The most serious consequences are enumerated in table 2.<sup>67-69</sup>

**Table 2.** Effect of gutkha on health

Clinical Changes		Functional Changes
Extra Oral	Intra Oral	Poor oral hygiene, <sup>37,72</sup> varying degree of trismus or inability to open the mouth, <sup>72,73</sup> speech, <sup>72,73</sup> swallowing, <sup>72,73</sup> reduced salivary outflow, <sup>72,73</sup> dysphagia, <sup>72,73</sup> hearing <sup>72,73</sup>
Sunken cheek <sup>72</sup>	Whitening of the oral mucosa <sup>72</sup>	
Stiff cheek <sup>72</sup>	Reduced and stiff oral aperture <sup>72,73</sup>	
Pseudo-proptosis <sup>72</sup>	Bald tongue <sup>72,74</sup>	
Multiple perioral skin folds <sup>72</sup>	Discoloration of the commissures <sup>72</sup>	
Pseudo malar prominence <sup>72</sup>	Retracted erythematous soft palate and uvula <sup>75</sup>	
	Forward pointing uvula <sup>72</sup>	
	Loss of tonsillar bulge <sup>72</sup>	
	Oral melanosis <sup>72</sup>	
	Chronic non healing ulcers <sup>72,74</sup>	
	Oral submucous fibrosis <sup>81,82</sup>	
	Oral cancer <sup>11,37,83</sup>	
	Calculus <sup>72</sup>	
	Discoloration of tooth <sup>78</sup>	
	Dental caries <sup>72,77</sup>	
	Attrition <sup>76</sup>	
	Erosion <sup>72</sup>	
	Extreme sensitivity in teeth <sup>37,72,76</sup>	
	Gingivitis <sup>79-81</sup>	
	Periodontitis <sup>13,80</sup>	
	Loss of gingivobuccal sulcus <sup>72</sup>	

**Table 3.** Description of acts against use of tobacco

Act	Description about act
Prevention of Food Adulteration Act (1954)	Required warnings on all chewing forms of tobacco
Drugs and Cosmetics Act (1940), and amendment rules, 1992	By this amendment, the central government banned the manufacturing and sale of toothpastes and toothpowders containing tobacco. The Supreme Court supported the ban, invoking Article 19 (6) of the Constitution in the public interest.
CCFS under Director-General of Health Services 29 Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	This committee recommended the appointment of a special expert committee at the central government level to ban chewing tobacco on health grounds
India's health warnings policy was drafted in 2006. It was came to force on 11 February 2007	The cigarette and other tobacco products (Prohibition of advertisement and regulation of trade and commerce production, supply and distribution) <sup>90</sup>
Order- S.O. 2815(E), dated: 28 November. 2008	Two pictorial warnings were rotated on cigarette packages and a separate warning was rotated on all smokeless tobacco products. (40% of principal area) <sup>91</sup>
Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	Specified health warnings to be displayed on all tobacco products packs (WEF. 31 may 2009) <sup>34</sup>
Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	New four pictorial warnings were rotated on cigarette packages and a separate warning was rotated on all smokeless tobacco products. Government amended it on 27 may 2011 and came into force in 1 December 2011. <sup>92</sup>
Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	On September 27, 2012, India proposed a new round of picture warnings that were to be required as of April 1, 2013, although implementation of these warnings varied. A set of 3 new pictorial warnings were developed for smoked tobacco products, and a separate set of 3 new warnings were developed for smokeless tobacco products. Health warnings were required to cover 40% of the front of all cigarette packages.
Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	On October 15, 2014, the government proposed larger warnings that cover 85% of the front and back of the pack.
Act, 2003 no. 34 of 2003, (The Gazette of India) Dated: 18 may 2003	The larger warnings were initially scheduled to come into effect from April 1, 2015, but the deadline was extended until April 1, 2016.

WEF: With effect from; CCFS: Central Committee for Food Standards

Long term use of gutkha affects general health leading to loss of concentration, loss of appetite, unusual sleep patterns, anemia, cardiovascular diseases (CVDs), stroke, head and neck cancers, and other cancers.<sup>22,44,51,70-72</sup>

### Why is the use of gutkha spreading?

Gutkha abuse is spreading due to its bright-color packaging, appealing fragrance, easy availability, and low price. It is popular among adolescents and low socioeconomic group. Now, symptoms of oral cancer are often appearing in very early age.<sup>51,57</sup>

In India, it has been observed that the tobacco industry has now shifted focus to advertising at point to sale outlets by exploiting loopholes in relevant portions of the cigarettes and other tobacco products act (COTPA).<sup>84,85</sup>

### What has been done? (Table 3)

In India, gutkha was temporarily banned in

March 2011 as its plastic packaging was found to be harmful to the environment.<sup>86</sup> After this, gutkha was banned under the Food Safety and Standards (Prohibition) Act (FSSA), 2006, section 30 (2) (a), Food Safety and Standards (Food Products Standards and Additives) Regulations, 2011 (Regulation 3.1.7), and Food Safety and Standards (Prohibition and Restrictions on Sales) Regulations, 2011 (Regulation 2.3.4) which ban any food product known to contain injurious adulterants like nicotine. The Indian government and Supreme Court argument for the ban was based on the association of these substances with cancer and oral potentially malignant disorders.<sup>11,37</sup>

Under Indian laws, gutkha is considered as a food item.<sup>85,87,88</sup> Some states like Kerala, Bihar, Madhya Pradesh, Maharashtra, Rajasthan, Jharkhand, Haryana, Delhi, Goa, Gujarat, Himachal Pradesh, Rajasthan, Punjab, and



Mizoram have stopped its sale, production, and supply.<sup>82</sup> The remaining states also are in the process like Andhra Pradesh, Assam, Chandigarh, Tamil Nadu, and Orissa. Until May 2013, 26 states banned gutkha.

### Campaign against gutkha ban

After some Indian states imposed the ban on the production and supply of gutkha, the tobacco industry launched an aggressive advertising drive against the ban. In the print media, a series of advertisements were released in cooperation with the Central Areca-nut and Cocoa Marketing and Processing Co-operation (CAMPCO), Smokeless Tobacco Association, and all India Kattha Factories Association.

### Discussion

Gutkha is a generic name of an Indian variant of smokeless tobacco with high level of carcinogens.<sup>31,45</sup> It is a common practice in south-east Asia for betel nut and tobacco chewing. Approximately 40% of the tobacco consumed in India is in smokeless form.<sup>88</sup> Consumption of chewing gutkha/pan masala are very common in India in almost all age groups, due to which many health related problems are arising rapidly.

The high concentration of nicotine in gutkha appears to be responsible for addiction.<sup>25</sup> TSNAs are potent carcinogens and their metabolism correlates with carcinogenesis.<sup>35,48,50</sup> The chemicals present in gutkha form ROS and affect the DNA repair pathways.<sup>89-91</sup>

Tobacco is one of the most important preventable risks to human health and an important cause of premature death worldwide.<sup>34</sup> Oral cancer has a vast potential for prevention,<sup>92</sup> accounting for up to 30%-40% of malignancies in India.<sup>93</sup>

For many years the gutkha companies have long evaded the government policies and sustained their business. They use the loopholes of law and policies, and are still manufacturing and marketing in some states as separate packing of tobacco and pan masala. The ban has been

imposed under the provision of centrally enacted FSSA 2006, section 30 (2) (a) and Food Safety and Standards regulations.<sup>82</sup> Now, the tobacco companies state that gutkha is not a food product.

Health experts and advertising industry members feel that the anti-tobacco movement and pictorial warnings on tobacco packs may not have desired impact on India, as the tobacco lobby is powerful in the country. The ban has only set in motion an increase in number of processes by altering the pattern of packaging, stocking, selling, and use of tobacco products.<sup>94</sup>

### What is required in the future?

With the anti-tobacco movement getting stronger on the one side and the tobacco lobby and the revenue on the other side, we should wait to see what steps are taken by the government.<sup>95</sup>

Effective comprehensive tobacco control laws that can impact on reduced consumption are needed. Rules and regulations with sufficient influential policies are required to clarify the role of tobacco use.<sup>96</sup>

The aim of this review was to increase the attention of government to complete ban of tobacco use, awareness, knowledge, and beliefs of public about the harms of not only gutkha but also all other tobacco products, and to promote the intentions to quit the habits.

### Conclusion

Gutkha consumption is quite alarming in present scenario. The widespread use of gutkha has attracted all age groups and genders, making it easier to chew tobacco without attached social sanction. This review is an effort to highlight the effects of Indian products of flavored tobacco clinically and functionally on human body.

### Conflict of Interests

The Authors have no conflict of interest.

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**تأثیر ژنوتوکسیک و کارسینوزنیک (سرطان‌زایی) گوتکا: یک نوع تنباکوی سریع‌الرشد بدون دود**

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**مقاله مروری****چکیده**

سرطان دهان نوعی بیماری بسیار کشنده و یکی از ناتوان‌کننده‌ترین و تغییر شکل‌دهنده‌ترین بدخیمی‌ها در دنیا می‌باشد. بر اساس گزارش سرطان دهان (GATS) Global Adult Tobacco Survey در سال ۲۰۱۰، ۶۰ درصد مصرف‌کنندگان تنباکو در هند فقط از تنباکوی بدون دود استفاده می‌کردند. در میان ۲۰۶ میلیون مصرف‌کننده تنباکوی بدون دود، ۶۵/۱ میلیون نفر از گوتکا استفاده می‌نمایند. در سال‌های اخیر، گوتکا به عنوان یک اختلال تهدیدکننده زندگی شناخته شده است که خطراتی جدی را برای سلامتی ایجاد می‌کند. هدف از انجام تحقیق حاضر، افزایش توجه به ممنوعیت کامل استفاده از تنباکو و همچنین، افزایش آگاهی، دانش و عقاید عمومی در مورد مضرات نه تنها گوتکا، بلکه تمام محصولات دیگر تنباکو و افزایش انگیزه برای ترک این عادت بود.

**واژگان کلیدی:** تنباکو، گوتکا، سرطان دهان، سرطان‌زا

**ارجاع:** تأثیر ژنوتوکسیک و کارسینوزنیک (سرطان‌زایی) گوتکا: یک نوع تنباکوی سریع‌الرشد بدون دود، سانخلا بیهارات، کاجواها خوشبو، حسین سید یاور، ساکسنا شیخا، سیرشا سانداراگیری کریشنا، بیهارگاوا آکشای. مجله اعتیاد و سلامت ۱۳۹۶؛ ۱۰ (۱): ۵۲-۶۳.

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