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Tobacco Constituents and Its Role in Cancer – A Review

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Introduction

Tobacco and mankind have been associated in the same way as food and tea since before history began. The tobacco plant is named after Jean Nicot, as he being the first to bring the tobacco in France, including snuff tobacco.[1]For hundreds of years, tobacco has been smoked, chewed, and inhaled in variousforms.[7]In India tobacco is used mainly for smoking and oral use while nasal use is relatively infrequent.Thetobacco plant, Nicotiana, has probably been responsible for more deaths than any other herb. At present, tobacco smoking is causing over 3 million deaths a year worldwide,and if current smoking trends continue the annual mortalitywill exceed 10 million by around 2030.[2]

In developing countries, cancer is among the ten most common causes of mortality.Oral cavity is the most common cancer site observed by Indian registries. Oral cancer is usuallyrelated to the use of tobacco in different forms. In India, the use of tobacco is common in forms ofchewing and smoking.The consumption of tobacco is closelyassociated not only with the development of oral cancer, but also with the course of disease evolving a poor prognosis. The most commonly used form of tobacco is the practice of chewing betel quid with added tobacco, which has been identified as a significant risk factor for developing oral cavity cancer.

Taxonomy

Kingdom – Plantae

Order - Solanales

Family – Solanaceae

Class - Magnoliopsida

Genus – Nicotina L.

Species – Nicotina Tabacum L.

Historical background of tobacco

The genus contains more than fifty species, but just two of them—tabacam and rustica—are taken into

consideration in this article. The size, shape of the leaves, and flower are the main physical distinctions between these two species. Both Nicotiana rustica and Nicotiana tabacum are native to North America and the West Indies, respectively. Tobacco differs from all other plants due to its nicotinic component. The volatile, colourless, oily liquid that makes up tobacco's active ingredient is an alkaloid that is toxic.[2]

About 10% of the dry weight of tobacco is made up of tobacco protein and amino acids. Alkaloids and volatile bases make up around 4% of the weight of tobacco. About 10% of the dry tobacco's weight is made up of waxes and resins, which can be extracted using ether. 7.8% of the tobacco weight is made up of metals (6.0%) and inorganic ions (1.8%). About 8 and 11% of the weight of dry tobacco is made up of phenolics and acids, respectively. [3]

Figure 1: The first published illustration of Nicotiana tabacum by Pena and De L'Obel, 1570–1571 (shrpiumadversana nova: London). The small illustration on the right of the picture shows how the Indians and sailors smoked Nicotiana leaves in a funnel [from New York Public Library with permission]

Compared to other herbs, the tobacco plant, Nicotiana, has likely caused the most fatalities. More than 3 million people die each year from tobacco use worldwide, and by 2030, if current smoking patterns continue, that number will rise to nearly 10 million.[3]

Forms of Tobacco

Smokeless Tobacco: Smokeless tobacco products can be divided into categories such as those used as dentifrice, for chewing, sucking, gargling, and sniffing.

The three forms of SLT that are most frequently used in the mouth are loose-leaf chewing tobacco, moist snuff, and dry snuff (Wahlberg and Ringberger, 1999). The majority of the plants used to make loose-leaf chewing tobacco are grown in Pennsylvania and Wisconsin. After being air-cured, the leaves are flaked and given a sweet flavour. Fire- and air-cured dark tobaccos that have been finely chopped make up moist snuff. [4]

Tobacco and tobacco smoke contain more than 120 alkanes, ranging from the C1 hydrocarbon methane to the C36 hydrocarbon hexatriacontane.[5]

Many of the higher molecular weight alkanes have been reported to be present in three isomeric forms, that is,

a) n-alkane H3C-(CH2)n-CH3

b) iso-alkane H3C-CH(CH3)-(CH2)n-1-CH3

c) anteiso-alkane H3C-CH2-CH(CH3)-(CH2)n-2-CH3

Smokeless tobacco is used in the forms of:[6]

a) Khaini - In the states of Gujarat and Maharashtra, a popular preparation called khaini is made by combining sun-dried tobacco and slaked lime.

b) Zarda – It is a mixture of tobacco, lime, spices, and sometimes silver flakes that is often added to pan and chewed.

c) Betel quid or pan –It is made up of four main ingredients: betel leaf (Piper betel), areca nut, catechu, and slaked lime, as well as tobacco. Spices and flavourings may also be added.

d) Kharra- it is a mixture of tobacco, areca nut, lime, and catechu that is frequently consumed by chewing in certain regions of Maharashtra.

e) Mainpuri –It is a type of tobacco preparation that is named after the Mainpuri district of Uttar Pradesh. It is made by combining tobacco with slaked lime, areca nut, camphor, and cloves.

f) Mawa – It is a combination of finely shaved areca nut, tobacco, and slaked lime, and is a popular choice in the state of Gujarat.

g) Gutka- It is also known as pan masala, is a pre-packaged form of tobacco that has gained widespread popularity throughout India due to its convenient packaging. It typically contains a mixture of areca nut, slaked lime, catechu, and tobacco, as well as additional flavorings and sweeteners that are added to enhance its taste.

h) Mishri – It is a teeth cleaning powder that contains tobacco.

i) Oral snuff is a type of tobacco product that consists of powdered tobacco moistened with a solution of natron (sodium sesquicarbonate). It is placed in the mouth, usually in the lower lip area or along the inner surface of the jawbone. Research has demonstrated that snuff contains carcinogenic compounds, such as N-nitrosamines, that originate from the tobacco used in its production.

Tobacco Smoke[8]

a) Bidi - Bidis are small, hand-rolled cigarettes made from sun-cured oriental tobacco flakes that are tightly rolled in a tendu leaf, which comes from a broad-leafed tree native to India.

b) Cigarettes - A type of smoking product that typically consists of finely cut tobacco leaves rolled in thin paper to form a small cylinder.

c) Nasal snuff- It is a type of flavored tobacco that is finely ground and meant to be inhaled through the nostrils.

d) The Chilam, or chillum, is a funnel-shaped container with a 500-700 ml capacity placed at the top of a hookah. The smoking mixture is placed above a small stone at the base of the Chilam, and then several pieces of glowing charcoal are added on top.

e) Kreteks – A type of cigarette that is made in Indonesia. it is made using mixture of tobacco,cloves,and other ingredients. Kreteks contain nicotine and many cancercausing chemicals that are harmful to both smokers and non-smokers.

f) Hookah – It is a type of water pipe that allows smoking of flavoured tobacco blends, including but not limited to apple, mint, cherry, chocolate, coconut, licorice, cappuccino, and watermelon.

g) Cigars are tobacco rolls wrapped in either leaf tobacco or a tobacco-containing substance, distinguishing them from cigarettes, which are tobacco rolls wrapped in paper or a non-tobacco-containing substance.

Chemical contents of tobacco:[4]

Tobacco smoke and its water-soluble components contain more than 300 carcinogens, including aromatic hydrocarbons, benzopyrene, and specific nitrosamines such as N-nitrosonornicotine (NNN), nitrosopyrrolidine (NYPR), nitrosodimethylamine (NDMA), and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK). Benzopyrene, which is present in cigarettes at a level of 20-40 mg per cigarette, is a potent carcinogen. The mainstream smoke of a single cigarette contains 310 mg of NNN and 150 ng of NNK. These carcinogens affect

keratinocytes and stem cells locally, as well as other tissues throughout the body after absorption.

For some products, long-term SLT usage carries a higher risk of oral cancer, much of which has been linked to the presence of TSNAs. The four main compounds are NNK, NNN, NAT, and NAB.

Green tobacco has extremely small amounts of TSNAs, but during curing, when amine alkaloids in the tobacco leaf react with either nitrite, which is created when bacteria reduce nitrate, or nitrous oxides, which are combustion byproducts of fire-curing, larger quantities of TSNAs are produced (Peele et al., 2001). While NNN, NAT, and NAB are created from their secondary amine precursors, nicotine (a tertiary amine) can be converted straight into NNN (nornicotine, anabasine, and anatabine, respectively). NNK, on the other hand, is solely created by nicotine.

Only two TSNAs, NNN and NNK, are considered to be potential carcinogens.

Mechanism of Tobacco Carcinogenesis[9]

The core pathway emphasises how important DNA adducts are in the development of cancer. This pathway involves prolonged exposure to toxins and ongoing cigarette smoking as a result of nicotine addiction. The carcinogens may undergo metabolic activation to create DNA-reacting intermediates that result in covalently bonded products called DNA adducts. The metabolic detoxification of carcinogens to safe excretion products competes with this. If cellular repair enzymes are able to remove the DNA adducts, DNA is restored to its original, undamaged state. However, if the adducts continue to accumulate during DNA replication, miscoding may take place, which results in a long-lasting change to the DNA sequence. Apoptosis allows cells with damaged or altered DNA to die. Loss of normal cellular growth-control regulation and tumour development may come from mutations in specific sections of important genes, such as the TP53 or CDKN2A tumor-suppressor genes, the RAS or MYC oncogenes, or the TP53 or MYC oncogenes.The serine threonine kinase AKT (also known as protein kinase B), protein kinase A (PKA), and other elements can be activated when nicotine and carcinogens bind directly to some cellular receptors. In turn, this may lead to a reduction in apoptosis, an increase in angiogenesis, and an increase in cell transformation.Additionally, tobacco products contain co-carcinogens and tumour promoters that may activate protein kinase C (PKC), activator protein 1 (AP1), or other factors, accelerating the carcinogenesis process.FHIT, fragile histidine triad; RB, the retinoblastoma gene

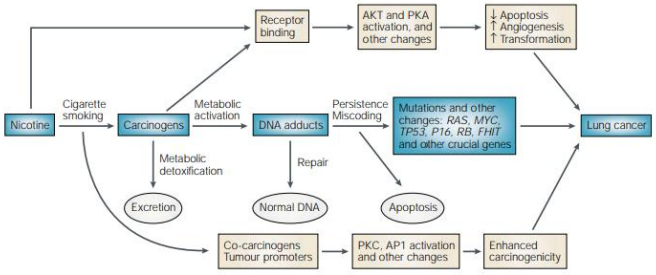

Fig 2: Mechanisms of tobacco carcinogenesis

Short summary of tobacco carcinogenesis

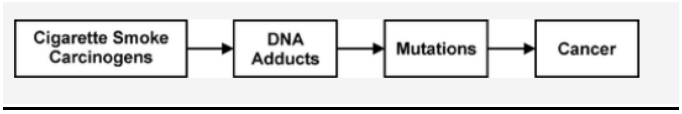

Fig.3: Short summary

Nicotine replacement therapy[10]

The optimum outcome for smokers is complete quitting. Even for people who have a strong wish to stop smoking, the highly addictive qualities of nicotine and the ritualistic behaviour of smoking present a significant obstacle.

In order to lessen the negative symptoms of nicotine withdrawal when quitting smoking, nicotine replacement therapy (NRT) is frequently employed.NRT has been developed and clinically validated in a variety of forms,

including chewing gum, transdermal and transmucosal patches, nasal sprays, and inhalers. Additionally, nicotine and nicotine analogues affect the brain's neural networks, which are suspected to have a role in a number of psychiatric and neurological illnesses.

Nicotine gum

The first NRT to be made available to customers was polacrilex, which contains nicotine given transmucosally.To release its nicotine, it is not chewed continuously for 30 minutes like regular chewing gum, but instead in short bursts as needed. Both a 2 mg and a 4 mg dose version are offered.More dependent smokers have been proven to have better success rates with the 4-mg gum than the 2-mg gum in quitting smoking.After a few weeks or months, the dosage is gradually decreased until it is no longer necessary.

[Brand names- Nicotex, Nicorette, Nicogum, Nicotinell, Zonnic]

Nicotine lozenge

The lozenge is offered in 2mg and 4mg dosage forms. The lozenge's usage and dosage instructions are similar to those for nicotine gum, however unlike nicotine gum, it dissolves in the mouth over the course of around 30 minutes, with some individual variation.Similar to nicotine gum, the lozenge's nicotine is slowly absorbed by the buccal mucosa and released into the bloodstream.

The lozenge provides an alternative to the gum for persons who need intermittent and controllable nicotine dosing, but who do not find gum chewing acceptable. Compared to gum, the amount of nicotine absorbed from each lozenge seems to be a little bit higher.

[Brand names- Commit® lozenges, Nicorette®lozenges, Nicotinell]

Nicotine sublingual tablet:

The nicotine in the tablet is absorbed sublingually when the medication is held under the tongue. The pill has the benefit of not needing to be chewed, just like the lozenge.The nicotine levels attained using the 2 mg lozenge and 2 mg sublingual tablet are comparable. Smokers are advised to utilise the product for a minimum of 12 weeks. The amount of tablets taken should be gradually reduced after 12 weeks.

[Brand names- Nicorette microtab]

Nicotine transdermal patch

It has been demonstrated that giving patients nicotine by injection or skin patches dramatically enhances their attention, learning, and memory.

You can stop smoking with the use of nicotine skin patches. The nicotine in the patch is absorbed through the skin and into the bloodstream.This substitutes the nicotine you would obtain from smoking and lessens the withdrawal symptoms associated with quitting. Over time, the nicotine content decreases until use is discontinued.

The patch's outer portion, which has an adhesive, is what adheres to the skin and keeps the patch in place. In order to effectively release and distribute nicotine, the inside portion of the patch—which carries the drug—must be pushed against the skin.

[Brand names - Nicoderm® CQ Patch, Nicotrol® Patch]

Nicotine oral inhaler

It consists of a mouthpiece and a nicotine-filled plastic cartridge. The hand-to-mouth ritual was one of the behavioural components of smoking that the vapour inhaler was created to meet, and it also delivers nicotine to lessen the physical withdrawal symptoms brought on by quitting tobacco.. Although referred to as a "inhaler," it is important to note that the majority of nicotine is delivered into the mouth (36%) as well as the oesophagus and stomach (36%).

Very little nicotine is delivered to the lung (4%). Because absorption is primarily through the oral mucosa, the rate

of absorption is similar to that of nicotine gum.Each inhaler cartridge has 10 mg of nicotine, of which 2 mg can be absorbed with repeated "puffing" and up to 4 mg can be administered. Each inhaler cartridge has 10 mg of nicotine, of which 2 mg can be absorbed with repeated "puffing" and up to 4 mg can be administered.

[Brand names- Nicotrol® Inhaler]

Nicotine nasal spray

It was made to deliver nicotine doses more quickly. The consumer product is a multi-dose bottle with a nozzle and a pump mechanism that dispenses 0.5 mg of nicotine per 50 uL of squirt. Two nasal sprays, one for each nostril, make up each dose.Compared to all other NRT forms, nicotine nasal spray rapidly enters the blood. Patients should begin receiving one or two doses per hour, with a daily dose limit of 40 doses. The average plasma concentrations are 8mg/ml after 10 hours of using a nasal spray containing 1mg of nicotine per hour.

[Brand names- Nicotrol®NS]

E-Cigarettes[11]

The newest and most promising devices for THR are electronic cigarettes (ECs) [Polosa et al. 2013b]. These electrically powered gadgets have a battery component (often a lithium battery) and an atomizer where liquid is held and produced into aerosol by heating and applying energy to a resistance encircling a wick. The primary ingredients in the liquid are propylene glycol, glycerol, distilled water, flavourings (which may or may not be permitted for use in food), and nicotine.

Currently, there are primarily three types of devices available. [Dawkins, 2013]

1) First-generation devices, typically resembling conventional cigarettes in size and appearance and made up of tiny lithium batteries and cartomizers (i.e. cartridges, which are usually prefilled with a liquid that bathes the atomizer). Batteries might be rechargeable or disposable (meant to be used just once).

2) Second-generation devices, consisting primarily of lithium batteries with increased capacity and refillable atomizers (sold in separate bottles). Modern atomizers allow you to easily swap out the atomizer head (resistance and wick) while preserving the body, which lowers operating costs.

3) Third-generation devices (also called 'Mods', from modifications)utilising extremely large lithium batteries that have integrated circuits that let users adjust the voltage or power (wattage) sent to the atomizer.

Figure 4: Examples of electronic cigarette devices currently available on the market.

[Brand names-Innokin, SMOK, Aspire, Voopoo, Uwell, Geekvape, Elf Bar, Vaporesso, Freemax, Wotofo.]

Nicotine vaccines[12]

Currently being researched are nicotine vaccinations, a novel technique to treating nicotine dependence. Nicotine is attached to a carrier protein in order to trigger the required immune response because it is a tiny molecule and an incomplete antigen. The immune system can be trained to detect nicotine as a foreign substance and to create an immunological defence against the drug by using nicotine-based vaccinations. Vaccines may do this by limiting the quantity of nicotine that enters the brain.

Conclusion

SLT use is causally linked to a high prevalence of oral cancer in India, where tobacco use involves not just

smoking but also using a variety of SLT products. SLT users are exposed to a wide range of toxicants, carcinogens, co-carcinogens, and tumour promoters. Millions of workers in the bidding sector are exposed to smoke on the job, which is another factor.The link between tobacco use and a variety of cancers has been conclusively demonstrated by epidemiological studies. New methods for cancer prevention will be developed as our knowledge of the pertinent carcinogenic pathways grows.

The first lines of defence against the rising tide of cigarette-related malignancies are now tobacco prevention and quitting.By defining carcinogen dose and biological effects in humans, identifying and targeting susceptible individuals, and influencing public policy, we may be able to create complementary and more widely accepted preventive approaches as our understanding of the mechanisms by which tobacco products cause cancer.

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