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Role of Chromium Enriched Tobacco in the Occurrence of Oral Carcinogenesis

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ABSTRACT

Cancer is a disease of major concern grasping the entire globe. It is one of the diseases characterized by high rates of incidence and mortality. Among all the cancer types, oral cancer has a high occurrence in countries like India, where people are more inclined towards the use of tobacco either for smoking or for chewing purpose. *Nicotianatabacum* being a hyperaccumulator plant can thus accumulate high amount of heavy metals in its parts, mostly leaves. The carcinogenicity of tobacco may be linked to the high concentrations of metals present in it. The presence of chromium in the trivalent or Cr(III) form in the leaves of the tobacco plant is ignored assuming it to be non-toxic. However, smoking or chewing tobacco can lead to the conversion of Cr(III) to the toxic Cr(VI) as hypothesized in the current review. The paper in its current form discusses the process of aggregation of chromium in the above-ground parts of the tobacco plant. The rhizospheric factors that promote the metal uptake by the plant are also discussed. The notion that Cr in tobacco is harmless has been argued upon. The paper proposes the role of Cr enriched tobacco in causing oral cancer and predicts the probable underlying mechanism. It emphasizes on the need to regulate rhizospheric factors, to prevent the accumulation of high concentration of the toxic heavy metal in the biomass of the tobacco plant.

Key Words: Cancer, Chromium, Heavy metal, Mutation, Rhizosphere, Tobacco

INTRODUCTION

Cancer is one of the leading global diseases responsible for high incidence and mortality rates. In terms of the number of deaths, it lies second only to cardiovascular disease accounting for 16% of mortality (Fig.1). As per the 2018 GLOBOCAN statistics, one out of five males and one out of six females are found to suffer from cancer, while one out of eight males and one out of eleven females die of the disease.¹ Cancer of the lip and oral cavity is the second most common cancer in India as far as the incidence (10.4%) and mortality rates (9.3%) are concerned.² Oral cancer is caused due to addiction habits and Human Papilloma Virus (HPV). However, majority of oral cancer in India is caused due to consumption of tobacco products either in form of smoking or non-smoke forms and account for 80-90% of cases.^{3,4} Indian Council of Medical Research (ICMR) has reported that 30% of all cancers in India are mainly caused due to tobacco. Among the tobacco linked cancers, oral cancer is the most frequent type in India and is responsible for approximately 42% of deaths in males.⁵

Tobacco has been reported to contain high levels of metal possibly resulting in an increased risk of exposure of these toxic components to the smokers and consumers of various products of smokeless tobacco. The toxic effect of these carcinogenic metals present in tobacco depends on the dose and the time of exposure. These toxic metals and metalloids present in tobacco are poorly studied and the mechanism behind their toxicity remains unexplained.⁶ Among several chemical compounds present in tobacco, 11 of these are metals or metalloids. An expert panel on tobacco regulation constituted by WHO prioritized four of the heavy metals like nickel, cadmium, arsenic, and lead in tobacco and tobacco smoke as of serious concern.⁷ The tobacco constituents are mostly related to several diseases especially cancer.

Chromium is a toxic heavy metal present in tobacco but its role in carcinogenesis is poorly understood and therefore ignored. The current review explains the probable role of hexavalent chromium generated from tobacco consumption and smoking in oral carcinogenesis. The authors have put

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forward a hypothetical model predicting the possible pathway of Cr(VI) involvement in oral carcinogenesis.

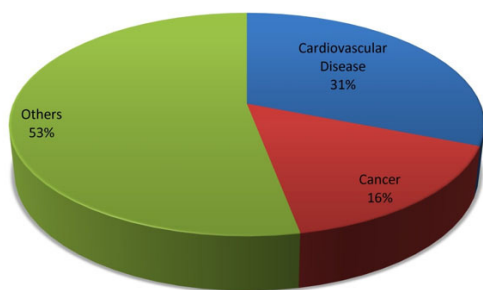


Figure 1: Two leading diseases with the highest global mortality rate.

Chromium in oral carcinogenesis

Chromium, unlike other toxic heavy metals, is available in several oxidation states, out of which, the trivalent or Cr(III) and the hexavalent or Cr(VI) are the two highly stable forms.⁸ Cr(VI) is considered to be a carcinogen because of its several toxic effects on the living biota including humans.^{9,10} Chromium remains a chief constituent of tobacco. It is mostly found in the trivalent form in tobacco products and therefore is not regarded as toxic. However, the inter-conversion of Cr in tobacco smoke and non-smoke form and its role in carcinogenesis has been poorly understood.

Sources of Cr in the environment

Cr mainly occurs from two sources – natural and anthropogenic (Fig.2). Cr occurs naturally over the earth crust in rocks, soil, water streams, and volcanic dust. It generally remains as Cr(III) bound to primary rocks and other metal oxides like iron.¹¹ Anthropogenic sources are mostly responsible in increasing the toxic load of Cr(VI) in the environment and can be further categorized into direct and indirect sources. The direct sources include industrial operations like mining, leather tanning, chrome plating, wood preservation, and production of paints, pigments, dyes, paper, and pulp.⁸ Water treatment plants, Portland cement, dumping of wastes and effluents, incineration of wastes, coke ovens, and cooling towers are some of the indirect sources of environmental Cr(VI).¹² Dumping of Cr rich solid and liquid wastes mainly contribute towards environmental toxicity.

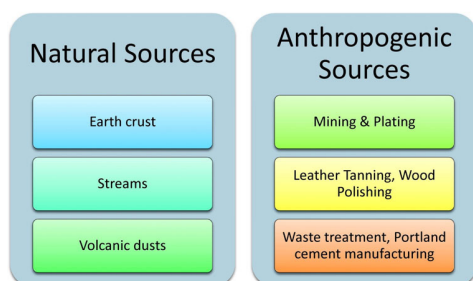


Figure 2: Sources of chromium (Cr) in the environment.

Cr(VI) and human carcinogenicity

The chemical structure of Cr(VI) plays a major role in facilitating its entry into human cells and thereby causing toxic effects (Fig.3). Cr(VI) mostly exist in the form of oxyanion (CrO_4) which structurally resembles that of sulphate oxyanions (SO_4). This structural resemblance allows Cr(VI) to use sulphate transporters present on the cell surface to enter the cells.¹⁴ Cr(VI) is mutagenic to human cells and is responsible for causing genotoxicity. It leads to the formation of DNA adducts which includes DNA-proteins crosslinks and DNA-aminoacids crosslinks¹⁵ which in turn inhibits DNA replication process. Cr(VI) also creates genomic instability by causing double-strand DNA breaks¹⁶. Cr(VI) causes epigenetic silencing, mutations, thereby leading to loss of mismatch repair mechanism¹⁶. The toxic form of the heavy metal induces chromosomal instability and abnormalities thereby causing DNA lesions¹⁷. Cr(VI) has been found to alter gene expression and actively induce the development of cancer through several mechanisms. It has also been found to actively participate in DNA methylation and gene silencing thereby leading to several types of cancer¹⁸. Cr(VI) is also believed to have a certain influence on microRNAs. The microRNAs play an active role in gene regulation and are often found to be dysregulated in Cr(VI) carcinogenesis thereby affecting important biological processes^{19,20}.

Chromium in Tobacco: *Nicotianatabacum* as a metal accumulator

Plants can uptake essential elements from the soil and utilize them as nutrients. However, certain plants can aggregate high metal concentrations in their biomass and are referred to as hyperaccumulators¹². Such plants are used to clean up soils contaminated with heavy metals by the process known as phytoremediation²¹. Similar metal accumulation ability by *Nicotianatabacum* plant makes it a viable option for metal removal from contaminated soils. However, such ability of the tobacco plant becomes a threat to health. *Nicotianatabacum* can uptake several heavy metals from the soil which includes cadmium, aluminium, arsenic, chromium, nickel, copper, zinc, lead and mercury. These metals are uptaken by the roots and then translocated and stored in the above-ground parts of the plant, mostly leaves. Cr is mostly up taken from the soil and translocated to aerial parts of the tobacco plant in its hexavalent state. The transport of Cr(VI) from roots to shoot is an active process and occurs through sulphate or phosphate channels²². Once Cr(VI) reaches the leaves, it gets reduced to Cr(III) by binding to specific ligands and sequestered into leaf vacuoles²³ of the tobacco plant where it is stored as Cr(III).

Chromium accumulation and factors governing its bioavailability for uptake

Accumulation of Cr(VI) in hyperaccumulator plants like *Nicotianatabacum* is highly dependent on several rhizospheric

soil factors like redox potential, pH, organic content, and availability of suitable microorganisms²⁴.

The redox potential (Eh) of soil provides idea on the oxidation and reduction nature of the soil and plays a pivotal role in bioavailability and speciation of Cr(VI) in the soil. At high soil Eh values, generally, an oxidation reaction occurs^{25,26}. Soils with high Eh values can cause the Cr(III) present in the soil to get oxidized to highly mobile Cr(VI), thereby increasing its availability in the soil for uptake by the plant.

Soil pH also is an important factor in metal availability to plants. Metals are highly soluble and mobile in acidic pH and are precipitated over alkaline soil conditions²⁷. However, the same does not apply to Cr and its bioavailability under varied pH conditions depends on the form in which it is present in the soil. Cr(VI) mostly exists in the anionic form (CrO_4^{2-} and HCrO_4^{-}) in the soil. Its bioavailability and mobility increases under high pH conditions and the reverse happen at low pH. At high pH, the hydroxyl ions increase providing the soil with a net negative charge and thereby decreasing sorption of Cr(VI)²⁸.

Soil organic matter content also plays a vital role in the movement and availability of Cr(VI)²⁹. Presence of soil organic matter lowers the soil pH making it acidic and thus increasing H^+ ion concentrations. This positive charge of the soil helps in retention or adsorption of Cr(VI) to soil matrix³⁰. Moreover, organic matter creates a reduced condition in the soil and also favours the growth of microorganisms. Therefore, Cr (VI) is reduced in two different ways catalysed in the presence of soil organic content. Firstly organic content of the soil creates reduced conditions that directly reduces Cr(VI) to Cr(III)³¹. Secondly, it favours microbial growth indirectly leading to reduction of Cr(VI) to Cr(III) as a result of biotic interaction between the microbes and the heavy metal³².

The rhizosphere soil due to its high nutrient concentration forms a favourable habitat for the growth of microorganisms. The microorganisms mostly bacteria have been found to play a major role in enhancing soil fertility and sustaining plant growth by processes such as mineralization, decomposition, nutrient immobilization, and nitrogen fixation³³. As far as the biogeochemical activity of heavy metals in the plant-soil rhizosphere is concerned, microbes indeed play an influential role^{34,35}. Several groups of microorganisms having the ability to reduce Cr(VI) to Cr(III) have been identified³⁶. These include bacteria³⁷, algae³⁸, fungi³⁹, and yeast⁴⁰. Microbial reduction of Cr(VI) to Cr(III) highly relies on the microbial strain, concentration of chromium, pH, and temperature of the soil^{41,42}.

Soil conditions like high redox potential, high pH, low organic content, and high soil temperature are the driving force for successful accumulation of Cr(VI) by tobacco plant and need to be regulated accordingly.

Cr(VI) rich tobacco in oral cancer: A hypothesized model

Chromium is a chief constituent in tobacco which may be attributed to the hyperaccumulation ability of the tobacco plant under favourable conditions. Cr is found in the trivalent form in tobacco and therefore not considered to be toxic by several researchers. The authors in the current review however have put forward contrasting views. The manuscript in its current form strongly advocates the probable involvement of Cr(VI) rich tobacco in oral cancer. A hypothetical model explaining the probable mechanism underlying oral carcinogenesis due to the presence of chromium in tobacco has been put forward.

The tobacco plant has been known to accumulate heavy metals like Cr in its aerial parts, mostly leaves. The leaves of the plant accumulate the heavy metal in its trivalent (non-toxic) form. Therefore, Cr(III) is not considered as a carcinogen in tobacco. However, there is always a chance that the non-toxic Cr(III) may get oxidized to the toxic Cr(VI) under favourable conditions thus promoting carcinogenesis. Cr(III) and Cr(VI) are the two most stable states of Cr that can interchange their oxidation states by undergoing redox reactions under conditions like metal content, presence of oxygen, high temperature, and moisture. Tobacco leaves in addition to Cr also contain manganese (Mn) which further oxidizes the less toxic Cr(III) to the highly toxic Cr(VI). During smoking of tobacco, the Cr(III) present in it may get oxidized to Cr(VI) due to the combustion of tobacco that involves oxygen and high temperature. Moreover, tobacco smoke when inhaled through mouth or nose gets mixed up with moisture thereby also leading to the formation of Cr(VI). Cr(VI) toxicity not only spreads from tobacco smoke but also smokeless forms. Tobacco, when taken in chewable form, gets in contact with oxygen and moisture thereby converting the elemental manganese present in it into MnO_2 , that catalyses the oxidation of Cr(III) to Cr(VI)(Fig.3).

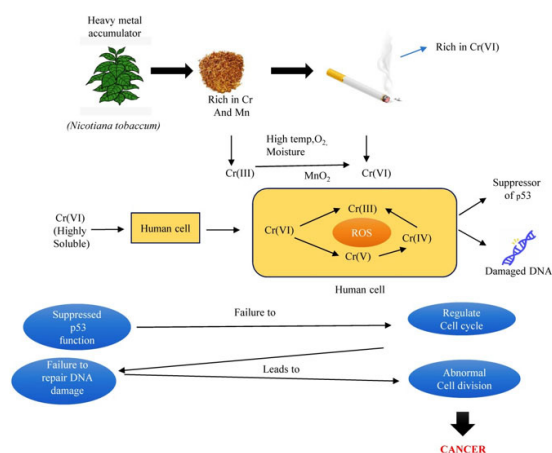


Figure 3: Mechanism underlying role of chromium enriched tobacco in causing oral cancer

The oral cavity being the first point of contact of both smoking and non-smoking form of tobacco products is hence more exposed to Cr(VI) and most probably its toxic impacts like the occurrence of oral cancer. Cr(VI) being highly mobile and permeable easily passes through the human cell membrane. Cr(VI) generated from cigarette smoke or chewing of tobacco can easily get absorbed into the squamous epithelial cells present in the internal surface of the oral cavity. Once Cr(VI) enters into the cells, it undergoes detoxification. Cr(VI) either gets reduced to Cr(III) directly or indirectly in a stepwise manner. In the indirect reduction process Cr(VI) gets converted to Cr(III) via several intermediates like Cr(V) and Cr(IV). During the reduction, the different species of chromium produce intracellular reactive oxygen species (ROS). Chemical compounds present in the cells like ascorbic acid and glutathione act as ROS scavengers thereby reducing Cr(VI) to Cr(III) and in the process lead to the production of free radicals (hydroxyl radicals)⁴³. Production of hydroxyl radicals inside the cells occurs in the presence of H₂O₂ through a Fenton-like reaction⁴⁴. ROS in the form of hydroxyl radicals can activate various pathways like apoptosis⁴⁵. Cr(VI) reduction inside the cells can also directly cause damage to the DNA by interacting with the proteins, amino acids, and even the DNA directly leading to single or double-strand breakage⁴⁶. Cr(VI) after reduction to Cr(III) can form bulky binary and ternary DNA adducts, thereby causing severe damage due to mutations⁴⁷.

Cr(VI) induced oxidative damage mostly occurs to the DNA of p⁵³ gene⁴⁸ present in the oral squamous cells thereby affecting the gene function. Being a tumour suppressor gene, p⁵³ works as a control centre of the cell and regulates the activity of several genes under stress conditions and also is involved in DNA repair. Damage to this gene leads to failure of repair mechanism in DNA of the oral epithelial cells, thereby resulting in mutations, uncontrolled cell division and finally cancer of the oral cavity.

CONCLUSION

Tobacco consumption remains a significant threat to public health around the world and smoking-related diseases are considered the world's most preventable cause of death.

Consumption of tobacco causes a significant threat to public health. Tobacco-related diseases are linked to the world's most prevalent cause of death. Tobacco has several carcinogens. Chromium has a strong link with the carcinogenesis of oral cancer. Cr(VI) is a toxic heavy metal that arises from several anthropogenic activities. *Nicotiana glauca* is a plant hyperaccumulator that can easily accumulate heavy metals like Cr(VI) in large quantities from contaminated soil and water bodies. This is the main reason behind the presence of the toxic heavy metal in tobacco and tobacco products.

Being a major component of tobacco, Cr(VI) has all the possibility of causing oral cancer by bringing about DNA mutations in the p⁵³ and other linked genes. The author(s) hereby advises preventing the accumulation of the toxic Cr(VI) in tobacco plant that is meant for commercial purposes to prevent the risk of oral carcinogenesis. This could be achieved by appropriately regulating the rhizospheric factors governing its uptake by the tobacco plant.

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