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Development of comprehensive data repository on chemicals present in smokeless tobacco products: Opportunities & challenges

Smokeless tobacco (SLT) products are consumed by 356 million people in 140 countries around the world[1]. Consumption of SLT products has been estimated to account for about 0.65 million deaths per year[2]. Worldwide, SLT products are consumed in varying forms ranging from simple cured tobacco to processed products with many chemical ingredients and additives[3,4]. Variations occur with the geographical location, type of tobacco plant, additives, flavouring agents, processing and curing methods[4,5]. Published reports highlight the chemical changes that a tobacco plant undergoes until the formation of final SLT product[5]. This creates product-wise and brand-wise variations in different SLT products.

Chemical profiling of SLT products has been attempted by some researchers[6-13]. A vital role of various chemicals has been indicated in the adverse health effects reported with SLT use[3,5,14]. Based on their carcinogenicity in experimental animals and humans, the International Agency for Research on Cancer (IARC) has classified SLT products as group 1 carcinogen (Carcinogenic to humans)[3,4]. Two of the chemicals found abundantly in SLT products, namely N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) belonging to the class of tobacco-specific nitrosamines (TSNAs) have also been classified in this group[3,5]. NNN and NNK are formed by the nitrosation of nicotine, the major tobacco alkaloid[15]. Nicotine is available in SLT products in predominantly two forms as follows: protonated and unprotonated[16]. Unprotonated/free nicotine, the amount of which varies according to the *p*H of the SLT product, can cross cell membranes readily[5,16]. Studies to estimate the *p*H and amount of total and free nicotine of various SLT products have been conducted[16-19]. However, a major drawback is the lack of comprehensive analysis of SLT products on a periodic basis. Most of the previous studies have been independent projects undertaken by different research groups focussing on one or two classes of chemical compounds only. These studies[7-10] depict variations in the amount of chemicals, *p*H and free nicotine content of SLT products. Thus, the need of the hour is to develop a one-stop repository compiling data on chemical analysis of SLT products from all the published studies. This will provide initial data for establishing priorities in research on chemical profiling of SLT products.

Opportunities in the field of chemical profiling of smokeless tobacco products

Available studies and reports on the chemical profiling of SLT products can be used to collect initial data[7-10]. Data on *p*H, moisture and free nicotine are also available from many reliable sources[17,19,20]. After compiling the available data, information about the physicochemical properties and protein targets of the chemicals can be obtained from freely available chemical databases such as PubChem[21], ChemSpider[22], BindingDB[23] and ChEMBL[24]. Further open source technologies, such as Linux, Apache, MySQL, PHP/Perl, cascading style sheets, HTML, JavaScript and Data Tables can be exploited for the development of online repository. The repository can then be equipped with built-in modules for data upload, simple search and browse options along with dashboards for different stakeholders.

Challenges towards development of repository on smokeless tobacco products

Although the literature is replete with studies on SLT products, a major bottleneck is the availability and distribution of the data in an organized fashion to allow for further analysis. Furthermore, the available studies cater to potent carcinogens (such as TSNAs

and polyaromatic hydrocarbons) with the scarcity of information about other chemical compounds[3,5]. One of the frequently used additives in SLT products, areca nut has been classified as a group 1 carcinogen[4]. Flavouring agents and other additives of SLT products have not been researched well. Moreover, the evolution of SLT products with the ever-increasing demand is making it difficult for researchers to study every SLT product in detail. Another significant challenge likely to be faced in the development of a repository of SLT product constituents is the absence of a standardized protocol of testing of these products and hence, the lack of comparability between studies.

Conclusion

Consumption of SLT products is a growing menace taking lives of millions of people worldwide. Evaluating the severity of the health effects of SLT products is a complex task mainly because of the variations in the products, their chemical composition and the differences in the mode of intake of these products. To effectively reduce the harm associated with SLT products, an important milestone will be the development of an online repository of chemical constituents of SLT products, as a one-stop information source on the carcinogenicity, physicochemical properties, protein targets and structural diversity of these chemicals. The repository will also provide initial data for developing regulations, guidelines and policies on the chemical composition of SLT products. Toxicokinetic studies can be utilized for identification of potentially harmful functional groups. The identified harmful groups can be replaced or removed to reduce the harm caused due to SLT products.

***Conflicts of Interest*:** None.

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