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A Review on 2,5 Dimethylfuran (Dmf) as a Chemical Marker to Quantify the Tobacco Smoke Exposure

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ABSTRACT:

Consumption of tobacco has always been a high-risk factor for many of oral and other related cancer in a country like India. Identifying various biomarkers present in an individual who is engaged in the activity of smoking carries the potential to limit the emergence of such diseases from occurring. 2,5-Dimethyl furan (DMF) as a biomarker has found to be of great interest among researchers because of its high specificity to tobacco combustion and sensitivity in detecting tobacco exposure. The current review article comprehensively evaluates multiple studies conducted so far, with a focus on 2,5-DMF, its identification from different /biological samples such as exhaled breath, blood, urine, and environmental tobacco smoke (ETS). It also highlights a critical discussion of various methodological aspects established for identifying the same biomarker in individuals who are engaged in the habit of smoking thus offering the readers to compare various methods for 2,5-DMF detection, also simultaneously offering insights into its potential for early detection and prevention of diseases related with tobacco consumption.

KEYWORDS: Tobacco consumption, 2,5-Dimethylfuran, biomarkers, breath, urine, blood, Environment tobacco smoke (ETS), coffee.

INTRODUCTION [1-6]

Many of us must be aware of the habit of smoking tobacco and its detrimental impact on our well-being, some of the major consequences include -Chronic obstructive respiratory disorder, cardiovascular diseases, its significant link with lung cancers as well as its association with various neurological diseases [1-4]. According to the World Health Organisation's 2008 report more than 5.4 million deaths per year including active smoking, smokeless tobacco use, and secondhand smoking occur due to diseases related to tobacco [5]. India alone accounts for 9.5% of overall deaths consuming more than 1 million adults each year because of tobacco use [6]. The tobacco usage especially the smoke form is quantified in pack-years, which is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. It is crucial to note that this calculation is purely based upon the history or the facts given by the user, which may sometimes be subject to potential falsification. Hence an objective way of measuring the exposure to smoke form of tobacco is required to identify the cause of such health challenges. Nicotine being a core compound in cigarette tobacco, has always sparked a profound interest in understanding its presence and impact on our well-being. However, shortly after inhalation of cigarette smoke nicotine starts to metabolize into numbers of its metabolites. Approximately 70-80% of the nicotine gets converted into cotinine, the conversion primarily occurs in the liver, influenced by the expression of the gene CTYP2A6 [7]. Thus, several studies in the past considered cotinine to be a reliable biomarker for detecting tobacco smoke exposure [8]. More than 4000 individual components have been identified from cigarette mainstream smoke and only a few of the components have been studied as biomarkers [9-10]. A multitude of

methods have been identified so far for the quantification of nicotine and its metabolite as biomarkers, through invasive and noninvasive means. The methods involve analyzing various biological samples such as blood, urine, saliva, and breath as well as a small percentage from hair follicles, toenails, gingival crevicular fluid, deciduous teeth, and breast milk [11]Among them Urine stands out to be more preferable biological fluid for the detection due to its higher specificity even in small concentration making it particularly more effective in assessing recent smoking[12-13]. However, due to reluctance by the participants from the former and potential psychological discomfort, the method itself poses challenges especially when employing it in larger populations [14] Selecting a breath sample as a sample of analysis has been brought up to be simple, noninvasive, less complex, and can be used as a method for the detection of tobacco smoke exposure to a wide range of compounds[15]. Several investigations have been conducted on the volatile organic components present in the exhaled breath of smokers, aiming to establish a correlation with both active and passive smoking statuses and also to identify early indicators that may carry potential risk for lung cancers [16]. Previous papers have reported changes in the levels of CO, benzene, toluene, and other volatile organic compounds (VOCs) in various biological samples. [17-18].The presence of 2,5 DMF has been taken to be the compound of interest due to its high specificity, thus resulting in a very low false positive rate[19]. The present review aims to provide a comprehensive overview of 2,5 DMF's history, chemical nature, it's assessment from various physiological sources with a focus on its association to smoking.

History:

2,5 DMF has long been regarded as a potential liquid biofuel due to its high energy density and derivation from renewable resources[20-22]. The identification of 2,5 DMF in the breath of a smoker traces back to 1990 when an investigator (Gordon 1990) was conducting an experiment to find the component biomarker in a smoker's breath via the gas chromatography-mass spectrometry (GC-MS) method of analysis. The results of his study concluded 2,5 DMF presence in 92% of the smoker's breath who were being examined [23]. Ever since then, efforts have been made in order to understand 2,5 DMF properties and its occurrence in various biological samples of a person who is engaged in the habit of smoking cigarettes. These attempts aim to explore novel and more efficient methods of analysis, while also concurrently advancing the field of health and dynamics.

Chemical Nature:

2,5-Dimethylfuran is a heterocyclic compound with the chemical formula C6H8O, classified as a furan derivative(Fig.1) .It is believed to be formed as a byproduct of pyrolysis of nicotine during the incomplete combustion of tobacco by replacing H at 2,5 positions by methyl groups from 2,5 Hexanedione [24].

- IUPAC name: 2,4-dimethylfuran
- Synonyms: 2,5-dimethylfuran, 2,5-DMF
- Octane no:119/high boiling point (92–94°C)
- lower water solubility (0.26%)
- mol wtg-96.13[25]
- Half-life: unknown but studies have identified a proportional increase in 2,5-DMF with benzene levels in human blood therefore the half-life of 2,5 DMF is believed to be similar to that of benzene which is eight hours in breath associated with the blood of a smoker [18].

2,5-DMF in association with smoking:

When tobacco undergoes combustion an array of more than 4000 chemicals can be identified formed during the process of pyrolysis. This combustion leads to the production of a number of volatile organic compounds (VOCs) which can be evaluated from the breath of the participant who is engaged in the habit of smoking habits [26-30]. Chromatographic analyses reveal the presence of various exogenous compounds from the breath of both active smokers, as well as secondhand smoke. The most commonly identified exogenous compounds from this analysis were benzene, xylene isomers, aromatic HC, toluene, and furan derivatives[18,27,31,32], among them over 40 compounds have been identified as having carcinogenic properties[33].Such substances mostly originate from cigarette smoke. Thus, they were identified more often in smokers 'and passive smokers 'breath than in exhaled air from non-smokers. Some of these analytes (e.g. benzene, 2,5-dimethylfuran, CO, few aromatic compounds) are toxic, and carcinogenic and might increase the probability of the appearance of lung cancer. Also, a large number of aromatic compounds in exhaled air from passive smokers can be also a reason for the increased risk of lung cancer [34]. Studies have incorporated Benzene levels as a biomarker for the detection of smoking status and it has been proven to be a reliable indicator, exhibiting its prevalence to be 10

times higher in a smoker compared to a nonsmoker. However, due to its large variability, along with it's detection in a breath of nonsmokers and many environmental sources it's use as a biomarker has recently constrained its utility as a promising biomarker [35]. In the search for the compound displaying a degree of similarity with benzene, the identification of 2,5-DMF stands out to be noteworthy in a person engaged in the habit of smoking. A study by Charles et al in 2007 documented the ratio of DMF to benzene 0.57 from the breath of individuals, whereas Gordon et al discovered the half-life of benzene and DMF in breath was similar to that in blood. Thus, reporting a strong correlation between the two chemical compounds' concentration in daily smokers [36].

Assessment of 2,5-DMF from various physiological samples:

Investigations have documented the presence of 2,5-dmf and its association with smoking tobacco cigarettes from environmental and biological samples. Table 1 to 5 describes the study's analytical methods and findings using the respective samples. However, the main objective of the authors is to highlight the effective application of the exhaled breath in quantifying the tobacco exposure in smokers. The presence of some of the VOCs in human breath is thought to be due to degradation of polyunsaturated fatty acids by oxidative stress. This process called lipid peroxidation is a chain reaction process in which reactive oxygen species (ROS) remove an allylic hydrogen atom from lipid membrane structures. This gives rise to a conjugated radical that is peroxidized by oxygen and this way prolongs the chain reaction. Among the final stable reaction products of this process are saturated hydrocarbons like ethane and pentane. These hydrocarbons enter the bloodstream and due to their low solubility in blood, they are excreted into breath within minutes after formation.

Table 1: Assessment of 2,5 DMF from Environmental tobacco smoke(ETS)

SAMPLE ANALYSED	ARTICLE LINK /AUTHORS	ANALYTIC METHOD	FINDINGS AND CONCLUSIONS
ETS	Monica Alonso, Anna Godayol, Enriqueta Anticó, Juan M. Sanchez.[37]	in-house capillary thermal desorption device connected to a GC-MS.	2,5-DMF was found to be highly specific, sensitive and quantitative markers of smoking contamination in indoor environment. No results were obtained indicating any association with the traffic pollutants emission product in outdoor environment, thus 2,5-DMF presence mainly not to be found in outdoor enviroment.
ETS	Gordon SM, Wallace LA, Brinkman MC, Callahan PJ, Kenny DV.[18]	Samples were subsequently analyzed by automated gas chromatography/mass spectrometry (GC/MS) using a modified version of U.S. EPA Method TO-14	No DMF was ever detected in blank samples. DMF was identified only in air samples where smoking occurred
ETS	Simone M. Charles, Chunrong Jia, Stuart A. Batterman, and Christopher Godwin[38]	Collected on desorption tubes packed with Tenax GR and Carbosieve SIII, samples were analyzed by GC/MS	DMF emissions differ by less than 10% from the average across various cigarette types. There was no noteworthy variation between light and regular tar cigarettes or between mentholated and non-mentholated cigarettes, although sample sizes for these comparisons were limited.

ETS	Xianqiang Fu, Diana Hernández, Dionna N. Attinson, Kalé Z. Kponee, Debra B artelli, Anna M. Gretz, Joshua N. Smith, Chunrong Jia [39]	TD-GC/MS-scan method and a TD-GC/MS-SIM method used,	A constant finding of 2,5-DMF in an environment with minimal and heavy smoking but not detected in a non-smoking outdoors or in house, thus indicating 2,5-DMF specificity to tobacco smoking and biomass burning smoke.
ETS	Ashley, D.L., Bonin, M.A., Hamar, B.,McGeehin.M [40]	TD-GC/MS	2,5-DMF reporting to be a significant component in gaseous phase of tobacco smoke.
ETS	Chunrong Jia, Stuart A Batterman, George E Relyea[41]	Collected in thermal desorption tubes followed by GC-MS for the analysis	2,5-DMF identified among numerous VOCs in cigarette smoke indoor but not in outdoor environment.

Table 2: Assessment of 2,5-DMF from breath

SAMPLE ANALYSED	ARTICLE LINK /AUTHORS	ANALYTIC METHOD	FINDINGS AND CONCLUSIONS
Breath	Sydney M Gordon, Lance A Wallace, Mariell e C Brinkman, Patric k J Callahan, and Donald V Kenny[18]	Breath samples were collected using a specially designed spirometer and cartridges containing Tenax GC adsorbent to trap the organic vapors.Analysed using thermal desorption technique followed by combined GC-MS.	Study identified 2,5-dimethylfuran and other compounds as effective biomarkers to accurately differentiate between smokers and non-smokers using breath analysis. It is also suggested to be a potential biomarker and could be appreciated as a reliable component by a non-invasive method of analysis for mass screening studies.
Breath	Thomas Hector Chappuis , Bao An Pham Ho, Morgan Ceillier, Florence Ricoul, Manuel Alessio, Jean-Francois Beche, Christelle Corne, Gérard Besson, Jérôme Vial, Didier Thiébaut, Bertrand Bourlon[42]	Presented the performances of silicon micro-preconcentrators chips for breath sampling. The silicon chips were coupled to a handheld battery-powered system for breath sampling and direct injection in a laboratory gas chromatography-mass spectrometry system through thermal desorption.	The concentration of benzene and toluene was found to be 10-100 times more in breath of smokers. Whereas, 2,5-dmf was only found in breath. Also a decrease of the three markers observed 20min after smoking.

Breath	Bogusław Buszewski, Agnieszka Ulanowska, Tomasz Ligor, Natalia Denderz, Anton Amann.[43]	Solid-phase microextraction (SPME) method was used for the measurements as an isolation and pre concentration technique.GC/MS for Identification and determination.	Identified fifty-six VOCs in all breath samples. Among them, 2.5-DMF presence was detected solely in the breath of smoking and passive smoking people.
Breath	Mar Castellanos , Rosa Suñer , José M Fernández-Real , Juan M Sanchez [44]	An “in-house” capillary thermal desorption device connected to a gas chromatograph with mass spectrometry detection (GC-MS)	2,5-DMF carrying the highest discriminant capacity for accurately determining the smoking status in comparison with toluene and xylene (AUC = 0.982, 95% confidence interval [CI]: 0.969–0.995), with a cut-off value of 0.016 ppbv (sensitivity = 0.965, specificity = 0.896).
Breath	Jaun M Sanchez, Richard D Sacks[45]	VOCs were collected and concentrated using a multihued sorption trap. For the sedation of a complex mixture of VOCs a multidimensional gas chromatograph(GC×GC), Detection and quantification of the separated VOC compounds done through a Time-of-flight mass spectrometer detector.	,5-DMF along with two new compounds (2-methyl- furan and furan) submitted as a potential breath biomarker for the detection of active smokers, was also reported to remain detectable in breath for more than 2 hours following active smoking.
Breath	Paweł Mochalski,Julian King, Martin Klieber,Karl Unterkofler,Hartmann Hinterhuber,Matthias Baumanne and Anton Amann.[46]	Gas chromatography with mass spectrometric detection (GC-MS) was utilised to identify and quantify volatile organic compounds in the blood and breath of healthy individuals, which were pre-concentrated using headspace solid phase micro-extraction (HS-SPME) and needle trap (NTDs) devices, respectively.	2,5-DMF revealed in higher abundance in exhaled breath and blood of smokers.
Breath	Diana Poli, Paolo Carbognani, Massimo Corradi, Matteo Goldoni, Olga Acampa, Bruno Balbi, Luca Bianchi, Michele	The subjects' breath was collected in a Teflon® bulb,pre-concentrated using a solid phase microextraction technique and subsequently analysed by means of gas cromatography/mass spectrometry.	Confirmed the assessment of compounds like 2,5-dmf,3-methylfuran,2-butanone ,octane ,decane only from a smoker’s breath and reported no relevance of them in breath of a non-smoking persons.

	Rusca & Antonio Mutti[47]		
Breath	Luigi Perbellini, Andrea Princivalle Marzia Cerpelloni, Francesco Pasini Francesco Brugnone[48]	Samples were collected and analysed by headspace and GC–mass spectrometry method.	3-Butadiene, 2,5-dimethylfuran and benzene levels were significantly higher in smokers than non-smokers in all biological media.

Table 3: Assessment of 2,5-DMF from blood

SAMPLE ANALYSED	ARTICLE LINK /AUTHORS	ANALYTIC METHOD	FINDINGS AND CONCLUSIONS
Blood	D. L. Ashley, M. A. Bonin, B. Hamar & M. McGeehin [40]	Hewlett-Packard Model 5890 was used for the gas chromatography, further the column was connected directly to the mass spectrometer via a heated interface.	2,5 DMF concentration in co-relation with the number of cigarette smoked, thus indicates for a proportional and a reliable biomarker for active smoking.
Blood	Chunrong Jia 1, Kenneth D Ward, Fawaz Mzayek, George Relyea.[24]	VOCs were concentrated by headspace solid-phase microextraction and then analyzed by gas chromatography/mass spectrometry with isotope dilution. The MS was operated in a selected ion monitoring (SIM) mode to minimize the interferences and chemical noise associated with whole-blood samples.	Blood DMF demonstrated a high sensitivity of 94% for identifying daily smokers and high specificity of 98-99% for the nonsmokers, however performed low sensitivity(26-28% in people who are not regular smokers), resulting in a higher likelihood of false negatives. Kappa data revealed a moderate level of agreement, with values ranging from 34-36%. Blood dmf showed similar effectiveness to serum cotinine for detection of individuals who ere actively engaged in daily cigarette smoking.
Blood	Paweł Mochalski, Julian King, Martin Klieber, Karl Unterkofler, Hart mann Hinterhuber, Matt hias Baumanne and An ton Amann[46]	Gas chromatography with mass spectrometric detection (GC-MS) was utilised to identify and quantify volatile organic compounds in the blood and breath of healthy individuals, which were pre-concentrated using headspace solid phase micro-extraction (HS-SPME) and needle trap (NTDs) devices, respectively.	2,5-DMF revealed higher abundance in exhaled breath and blood of smokers.

Table 4: Assessment of 2,5-DMF from coffee

SAMPLE ANALYSED	ARTICLE LINK /AUTHORS	FINDINGS AND CONCLUSIONS
Coffee	Castellanos M, Suñer R, Fernández-Real JM, Sanchez JM[44] Alonso M, Godayol A, Anticó E, Sanchez JM.[37]	During the study for identification of 2,5-DMF, coffee was the only potential variable that might affect the observed results.

Table 5: Assessment of 2,5-DMF from urine

SAMPLE ANALYSED	ARTICLE LINK /AUTHORS	ANALYTIC METHOD	FINDINGS AND CONCLUSIONS
Urine	Antônio Felipe F Oliveira, Patrícia P Maia, Maria José N Paiva, Maria Elisa P B Siqueira.[49]	Method using headspace solid-phase microextraction (HS-SPME) and gas chromatography (GC) equipped with a flame-ionization detector (FID) was developed.	2,5-Dimethylfuran along with 2,5-hexanedione, and y-valerolactone, were detected in the urine of (vinyl sandals) workers by gas chromatography. Also found that the markers retained in the body of workers exposed to n-hexane until the next working day.
Urine	L Perbellini, F Brugnone, G Faggionato.[50]	Urine samples were treated with β-glucuronidase, adjusted to pH 2, heated, and extracted with dichloromethane. Extracts were examined by gas chromatography with cyclohexanone as an internal standard.	2,5-Dimethylfuran in association with other metabolites were detected in human urine especially in workers exposed to n-hexane.

Roles:

The 2,5DMF exhibits a multitude of biological and chemical roles that include it's anti-fungal activity, its utilization as a metabolite in human urine, bacterial and plant systems, also a product in the Maillard reaction to mention, its application as a fumigant and source of high energy fuel.

Conclusion:

2,5-dimethylfuran and its presence in various physiological samples reveals to be a good biomarker for distinguishing a smoker from a nonsmoker, as well as a reliable indicator of smoking activity in any environmental setting. The analysis of 2,5-DMF seems to be simple, and rapid with improved specificity. Thus, serves to be a valuable asset for mass screening initiatives. Further studies undertaking 2,5-DMF as a biomarker of interest for individuals engaged in smoking, can accelerate the process of analysis, reduce the percentage of tobacco consumption, early detect tobacco-associated health hazards, and also foster a healthy environment, thus benefiting several individuals. 2,5-DMF being one of the VOCs, constructing a device that can help to detect the biomarker in the exhaled breath of a smoker as a non-invasive technique can be reliable, thus improving the method of detection, making the method more convenient for the participants as well as rapid, and cost-effective.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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