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VOLATILE ORGANIC COMPOUNDS AS A BIOMARKER OF TUBERCULOSIS

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Abstract

Tuberculosis is an extremely contagious disease which spread mycobacterium tuberculosis to several peoples surrounding to them. Diagnosis of tuberculosis at an early stage is a very inspiring job. Current diagnosis tools take lots of time to detect this disease, which convert it to frightful disease. As compare to traditional methods biosensors detect fast but less sensitive. Volatile organic compounds in breath are the biomarkers of active pulmonary tuberculosis. These biomarkers are generates from the metabolism of mycobacterium tuberculosis. There are four specific volatile organic compounds i.e. methyl nicotinate, methyl henylacetate, o-phenyl anisole, methyl p-anisate of tuberculosis which are present in breath. Detection of tuberculosis in breath is a non-invasive method which is beneficial for children and old age people. The amounts of these biomarkers are increase in tuberculosis positive patient as compare to negative patient. The main focus of this review is on volatile organic compounds which are the specific biomarkers for detection of tuberculosis.

Keywords—Mycobacterium Tuberculosis, Biomarker, Biosensor, Volatile Organic Compound

I. INTRODUCTION

Mycobacterium tuberculosis a most dangerous bacteria cause's tuberculosis. In the world tuberculosis becomes a most hazardous, risky, deadliest disease due to unsatisfactory detection techniques. As per world health organization every year millions of people were affected by tuberculosis and millions of people was death from this communicable disease [1, 2]. There is a step-wise growth of tuberculosis. At first step person is affected with tuberculosis bacteria, but the quantity of bacteria is very less since the symptoms were not clear. This stage is titled as latent tuberculosis. At the second step tuberculosis bacteria generates in large amount which affect human health. This stage is titled as active tuberculosis. If it is not detected in time it converts to drug resistant tuberculosis and further it converts to multi drug resistant tuberculosis. Drug resistant tuberculosis means tuberculosis bacteria are resistant to first line anti tuberculosis drug and multi drug resistant means tuberculosis bacteria are resistant to multiple anti tuberculosis drug. The bacteria of tuberculosis are spread through tiny airborne droplets through sneezing and coughing [3, 4]. These bacteria first affects to lungs and then extents to other organs of the body. If this disease is detected at early stage, it can be controlled else it convert to further frightful stage. The current available detection methods of tuberculosis are too prolonged and less sensitive. Therefore there is a strong requirement to find new detection method which is sensitive and fast. To develop a new recognition tools biomarkers play an essential role in decreasing the morbidity and mortality of tuberculosis.

The objective of this paper is to introduce the frightful disease tuberculosis, various traditional and biosensor detection technique and main focus of the review on volatile organic compounds which are the specific biomarkers for detection of tuberculosis.

II. TB BURDEN AND REDUCTION TARGET

As per the world health organization report, in 2018 near about 10 million people were infected with tuberculosis, 1.2 million people were deaths amongst HIV negative people and 251000 people were deaths amongst HIV positive people. Fig 1 shows region wise percentage of TB cases of 2018.

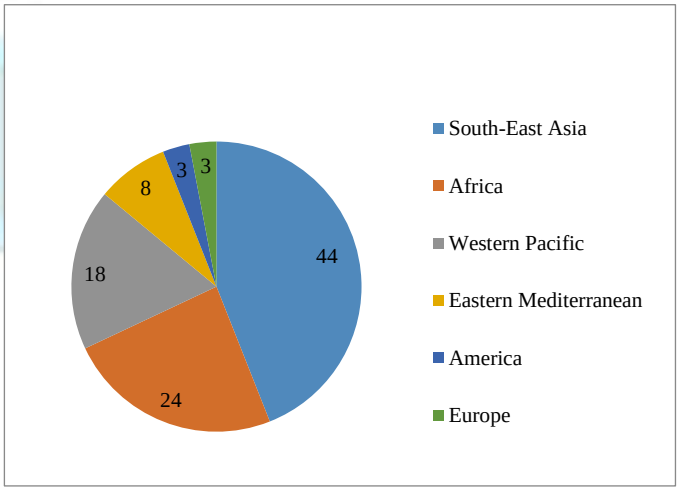

Fig. 1. Region wise percentage of TB cases of 2018

World Health Organization and Sustainable Development Goals set targets to reduce or to stop dangerous disease tuberculosis from world by 2030. Under the End TB strategy the reduction target of 2030 are set as 90% reduction in TB death rate and 80% reduction in TB incidence compared with levels in 2015. Fig 2 shows the milestone of reduction target [5].

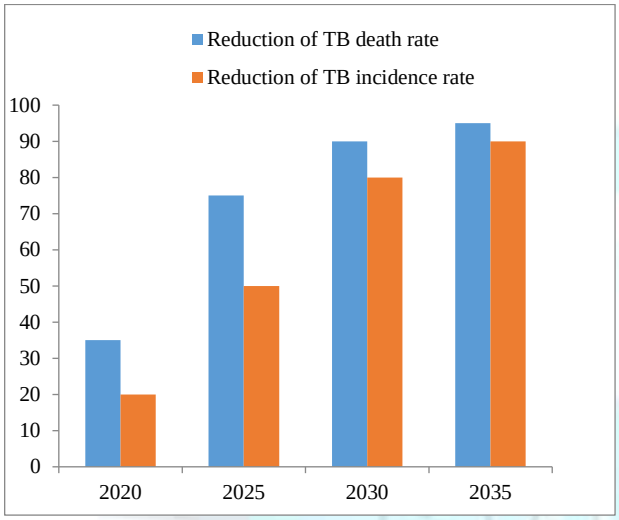

Fig. 2. Milestone of reduction target of TB death rate and incidence rate in percentage

III. Current Detection Techniques

Till date many researchers has developed various detection techniques, Some traditional techniques such as Immunological and microbiological tests as smear microscopy using Ziehl-Neelsen staining, Fluorescence microscopy uses auramine rhodamine staining, and Genotypic tests such as Polymerase chain reaction which intensifies DNA fragments which evaluated using Electrophoresis and Hybridization-based techniques. Most usable detection method is Radio-graphic which used x-ray to imagine the internal structure of a patient. But all these traditional diagnostic methods take long time to diagnose, required laboratories and trend persons, expensive and required strong resources and less sensitive [6]. Considering all these realities some researchers has developed various biosensors. Biosensor is a device which sense biological elements which used to diagnose physical as well as chemical substances. These biosensors based on signal transducer characterized as: electrochemical biosensor which detect the electrical signals with the help of physical or chemical interaction of functionalization surface of electrodes. M.tb cell wall elements elevated against the antibody of a single clone of cell can be restrained onto an electrode surface wide-open to a suspension of M.tb. Thus the interaction between the antibody and M.tb bacteria were detected by a change of conductance [7,8], magneto elastic biosensor sensed by pick-up coil and vibrates when magnetic field externally functional the rate of occurrence of resonant features [9], micro cantilever sensor bends when antigen-antibody interact with each other and it assist to detect the tuberculosis [10], and piezo-electric quartz crystal for diagnosis it linked between the changes in mass deposited on the electrodes and changes in the crystal frequency. There are two types of piezo electric biosensors as quartz crystal microbalance and multi-channel series piezoelectric quartz crystal. In quartz crystal microbalance, on the crystal electrodes the binding of M.tb cells were monitored in real time and the frequency shift was calculated. The multi-channel series piezoelectric quartz crystal depends on the diagnosis of volatiles formed by the development of M.tb such as NH_3 and CO_2 [11,12]. As compare to traditional technique biosensor is fast to detect and sense, but all the requirement of detection of tuberculosis were not satisfied using current biosensors. These biosensors are at developing stage. Table 1 shows the current available detection techniques.

TABLE I. Current Available Detection Techniques

Methods	Techniques
Traditional Detection Techniques	Ziehl-Neelsen staining
	Auramine rhodamine staining
	Genotypic tests
	Radio-graphic
Biosensors based Detection Techniques	Electrochemical biosensor
	Magneto elastic biosensor
	Micro cantilever sensor
	Piezo-electric quartz crystal

IV. Detection Through Volatile Organic Compound

There is an urgent requirement of easy and effortless technique for diagnosis of tuberculosis. Some researchers have designed non-invasive method for diagnosis of tuberculosis through breath samples. For this purpose volatile organic compounds were measured through breath. Metabolism of mycobacterium tuberculosis generates various volatile organic compounds. These volatile organic compounds are biomarkers of tuberculosis. In Mycobacterium tuberculosis infected patient the level of certain volatile organic compounds increases. These levels of certain volatile organic compounds were analyzed through breath.

A. Biomarkers

In standard biological practices, biomarkers are used to calculate and evaluated the presence of disease. The current status of patient can be recognized with the help of various biomarkers. Various diseases could be diagnosed through blood, sputum, urine, etc. To diagnose the status of patients with tuberculosis some non-invasive respiratory system were used. Metabolism of mycobacterium tuberculosis generates four volatile organic compounds i.e. methyl nicotinate, methyl henylacetate, o-phenyl anisole, methyl p-anisate which are specific biomarkers [13]. These biomarkers are found in human breath of active pulmonary tuberculosis which obtained from the contagious bacterium of mycobacterium tuberculosis [14]. In healthiest people the volume of these volatile organic compounds are at under certain quantity. In human breath these volatile organic compounds vary due to pulmonary tb, as mycobacterium contagion generates mycobacteria and oxidative pressure. Both produce unique volatile organic compounds [15]. Tuberculosis can be diagnosed using these specific VOC which generates by M.tb through breath test.

B. Sample Collection

A standard breath sample collection devices were used for exhaled breath collection. Online apparatuses are available for effortlessly gathering of exhaled breath samples. Some researchers used gas sampling bags and glass sampling bulbs for breath sample collection [16]. Exploration of Volatile organic compound from exhaled breath acts as an auspicious technique for non-invasive exposure of contagious diseases. For small children and severely affected patients this non-invasive breath analysis technique is more suitable than invasive techniques [17]. To focus on VOCs and to control test group factors various devices have been established onto the thermal desorption tubes and successively carrying those tubes for laboratory exploration.

C. Breath Sample Analysis

Breath samples which were collected in the various collection devices were investigated in the laboratory by automated thermal desorption by gas chromatography and mass spectroscopy. To detect dissimilar elements from the sample, the joint characteristics of gas chromatography and mass spectrometry were used. The various functions were performed by gas chromatography and mass spectrometry such as gas chromatography separates the individual elements from a mixture, transport the separated elements to the ionized compartment, ionized it, exploration of mass, ions detection using electron multiplier, acquiring data, processing and present using computer system. Chromatographic assay of breath and air were run with internal standard to enumerate principal regions and to control for implication in apparatus implementation [18]. Syhre et al. established that in pulmonary tuberculosis positive patient breath methyl nicotinate was increased as compared with negative patient [19]. Philips et al. established that volatile organic compounds range related with pulmonary tuberculosis, particularly methylated and non-methylated hydrocarbons, with methyl naphthalene and dimethyl cyclohexane allied amongst in vitro culture and in vivo breath samples [15]. Kim et al. for diagnosis of volatile biomarkers developed a nanotube based sensor which presents a metal functionalized titanium dioxide [20]. Many researchers were investigated breath samples to find the level of volatile organic compounds for detection of pulmonary tuberculosis.

CONCLUSION

Tuberculosis is a most dangerous communicable disease in the world. Every year millions of people were infected by this frightful disease. Due to the lack of detection techniques and in time treatment, the death rates of tuberculosis were increases. Detection at early stage is most important otherwise it converts to dreadful disease and transfers these bacteria to many other peoples. Current diagnostic tools i.e. traditional and biosensors are very slow, less sensitive and expensive. Metabolism of mycobacterium tuberculosis generates four volatile organic compounds i.e. methyl nicotinate, methyl henylacetate, o-phenyl anisole, methyl p-anisate which are specific biomarkers of tuberculosis. Diagnoses of these biomarkers in breath are non-invasive technique. Breath sample collection is easy especially for children and older patients. Detection of tuberculosis through volatile organic compounds which are biomarkers of tuberculosis in breath plays an essential role in decreasing the morbidity and mortality. But till date all biomarkers detection technique was not satisfied successfully. In future there is strong need to work on it and make it essential to stop TB from world.

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