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Review Article

Exhaled Volatile Organic Compounds (Vocs): A Potential Biomarkers for Chronic Disease Diagnosis -

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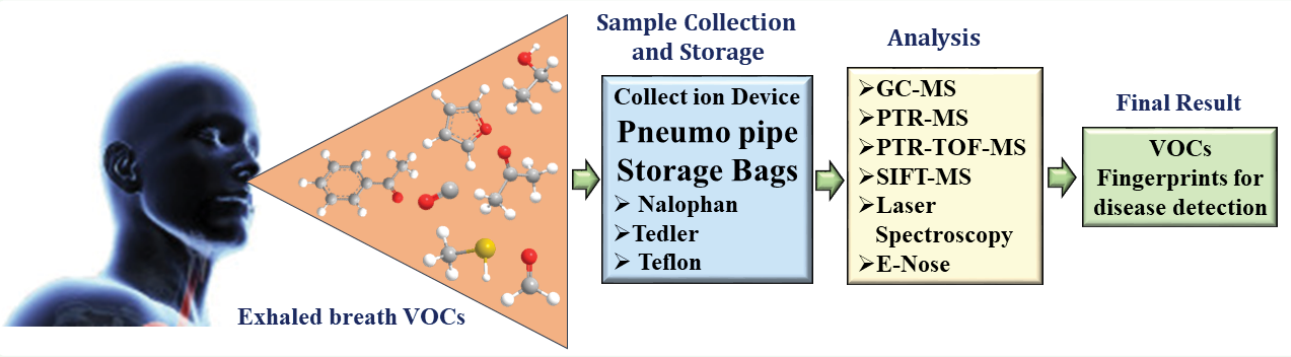
Abstract

Our exhaled breath is known to contain several Volatile Organic Compounds (VOCs) at very low concentration (ppm-ppv) including hydrocarbons, alcohols, aldehydes, ketones, esters etc. and other non volatile compounds. These VOCs have been correlated with various types of diseases though the concentration level of VOCs in exhaled breath varies depending upon individual's health status. Analysis of breath VOCs concentrations with a satisfactory precision can give an indicator of metabolic condition, allowing a difference between healthy and diseased states. Breath prints of VOCs provide fingerprints of diseases in discriminating healthy persons from patients and it is necessary to establish specific methods of sampling, sample preparation, and sample identification for every disease to get accurate information. Therefore identification of VOCs as a biomarker in exhaled breath could be useful method for assessing, diagnosing, and monitoring of different types of diseases including Covid-19. This Review presents an update on biomarkers of specific diseases with the systematic studies of biochemical synthesis of VOCs and also describes conventional and advance techniques of breath analysis as well as breath collection techniques for future prosperity in non-invasive biomedical perspectives.

Keywords: Biomarker; breath prints; exhaled breath; metabolomics; VOCs



INTRODUCTION

Biomarkers are those persistent bio-molecules which are present in soluble state in the cell sap or organ system of an individual. These unique metabolites are measured and assessed to investigate normal biological and pathogenic processes accounting the relationships between human health and environmental chemicals. In modern decades biomarkers play a crucial role in monitoring the physical condition, stress level, development of chronic human diseases and immune status of an individual. Curative biomedical interventions can be developed detecting the physiological responses to a specific or a set of biomarker [1-7]. A significant number of invasive techniques have been developed to detect such molecules present within body at micro, nano or picomole level by using selective dyes, adjuvants or spectral databases. But all these processes demand body fluid and excreta like sputum, blood, serum, amniotic fluid, spleen sap, etc. though these are little bit of faster and quite specific than earlier medical diagnostic processes [8]. These impose the challenge in monitoring the individual's health status in a daily basis and also at early stages of disease prognosis. So, the modern day biomedical system is in keen need to have absolute specific, very fast in assessment, regular monitor able in daily or even hourly basis at nono or picomole concentration and it must be free from any invasive procedures.

In this connection, the persistent Volatile Organic Compounds (VOCs) have been considered as very important in non-invasive techniques. In breath a huge number of bio-molecules have been identified as possible morbidity indicators and used to examine and diagnose the diseases including inflammations along with evaluation of the response to the treatment [9-11]. Some biomolecules in the exhaled breath are still in the innovation phase and only a few have been examined in observance with the Standards for Reporting of Diagnostic Accuracy (STARD) criteria [12-14]. In 460-370 BC, Hippocrates in his thesis first described unpleasant odour and hepatic fetor in breath smell [15-17]. Much later, in the second half of the 18th century, Antoine Lavoisier developed a new theory of combustion and he discovered Carbon Dioxide (CO_2) in the exhaled breath of guinea pigs. With this discovery, he also concluded that CO_2 is a sign of life [15]. After few years later, Wilhelm Petters in 1857, identified acetone in urine of a diabetic patient and also found an apple like odour in breath of diabetic patients [18,19]. Forty years later, Nebelthau first observed that continuous starvation yields the higher amount of acetone in exhaled breath [18], while very low of this amount is found in urine. Nowadays, it is well established that the average concentration of acetone in healthy non-starving persons is estimated to be around 0.4 ppm in comparison to 5.8 ppm in healthy starving persons [20]. The presence of mercaptans in the breath of patient with the rigorous liver disease was recognized by Davidson in the year of 1949 [21] and he also proposed 'fetor hepaticus' as the source of aroma [22]. Later on in 1960s, ethanol and acetonitrile have been identified in exhaled breath while methanol concentration in human breath ranges from 48 to 258 ppb. In the year of 1970, Chen. reported that breath of patients with liver cirrhosis contains volatile fatty acids. Cohen and coworkers (1974) identified and measured the small chain hydrocarbons, which are the products of lipid peroxidation and suggested that the concentration of these small chain hydrocarbon could be increased due to oxidative stress *in vivo* [17,23,24]. Nobel laureate Linus Pauling and co-workers have made a remarkable improvement in the field of breath analysis and opened the avenues of metabolic profiling, further known as "metabolomics" [25-27]. Researchers were inspired to undergo researches on Volatile Organic Compounds (VOCs) present in breath specific for particular diseases. Another significant study was reported by *Simenhoff*, et al. [28] that trimethylamine and dimethylamine are present in "uremic breath" of terminally ill patients with renal disease [29,30]. In the mean time some additional molecules such as ammonia were also measured in

human breath by Lovett, et al. in 1979. Antony Manolis (1983) was the first to present a comprehensive review on VOCs analyzing breath of marijuana smokers and reported on the different toxic compounds like 9-tetrahydrocannabinol or tetrachloroethylene [31]. Thus, exhaled VOCs present in human breath could be used as "breath-prints" that provide fingerprints of morbidity by discriminating healthy persons from the diseased [32,33]. Therefore, exhaled breath is a reasonable medium for detection of VOCs. After the generation of VOCs within the body via the blood and then they appear in exhaled breath by crossing the alveolar interface [34]. They can be measured in a very tracer concentration as low as inparts-per-million by volume (ppmv) and parts-per-billion by volume (ppbv). Although the trace VOCs are created in the oral cavities that do not essentially go through the blood stream, do appear on exhaled breath [35]. Therefore, investigation of breath VOCs concentrations with a satisfactory precision can give an indicator of metabolic condition, allowing a difference between healthy and morbid states [36]. Therefore, development of suitable techniques has the prospective to detect diseases in their premature stages, painlessly and non-invasively [36-39]. In addition to VOCs, a number of inorganic compounds such as nitric oxide, ammonia, hydrogen sulphide and carbon monoxide are also emerging in exhaled breath [40-43]. Therefore for assessing different diseases in a non-invasive manner these volatile compounds are very important [44]. As VOCs come from a variety of sources [45], it is necessary to establish specific methods of sampling, sample preparation, and sample identification for every disease to get accurate information.

In rapid clinical diagnosis breath analysis techniques remain quite less popular and neglected while compared to blood and urine analysis [46-48], though, biomedical engineers are working over the decades in this endeavour to increase the applications of breath analysis [49,50]. Recent published works have tried to established the relationship between certain diseases manifestation with the onset of VOCs [51,52]. Nowadays, scientists have identified many compounds by breath analysis which plays significant roles in development of symptoms in clinically active patients. For example, higher concentrations of acetone is present in diabetic patients; dimethylamine and triethylamine in patients with renal insufficiency [53,54]; and hydrogen sulphide in liver disease [55-61]. So far, biomarkers have been recognized for a variety of diseases such as breast cancer, liver cirrhosis, lung cancer, pulmonary tuberculosis, asthma and diabetes [62-66]. Over the last decade, research and development involving the analysis of breathe vividly focused on the detection of VOCs has been a target to develop the most sophisticated techniques for food industry and healthcare services [67-71].

In this review, we are mainly focusing on the chemical natures of different types of VOCs that can be potential biomarkers for detection of different diseases and biochemical or metabolic pathways of VOCs production as well as their disease specific detection techniques to popularize these unique bio-molecules as important standard reference chemicals to formulate non-invasive diagnostic tools for diseases.

Categories and Persistence of VOCs

An ample range of irregular VOCs identified as promising biomarkers of different human diseases are members of a large variety of organic chemical classes. Most of these belong to common chemical classes, *viz.* aldehydes, ketones, aliphatic hydrocarbons, aromatic hydrocarbons, heterocyclic hydrocarbons, sulphides, organic carboxylic acids, alcohols, ethers, esters, nitriles, and terpenoids or isoprenoids. They have different physicochemical properties that mostly determine their distribution, adverse effects and also mechanisms and rates of discharge from the body viaexhaled breath [49]. Different volatile organic compounds and their corresponding metabolic basis are illustrated in table 1.

The concentration of a number of VOCs present in breath ranges in between 1-10 ppb are 2-hexene, butane, *cis*- and *trans*-2-butene, isobutyl alcohol, capryl alcohol, 1,1,1-trichloroethane, butyl acetate, *n*-butyl alcohol, pentanal, indene, methyl isobutyl ketone, propanal, and ethyl benzene. Several studies identify health, habits (such as smoking, chewing tobacco, alcohol drink, etc.) and occupational exposure of persons as the strongbreath emission influences(85, 86).For example, chlorinated and aromatic hydrocarbons including the breath of persons with high professional exposures have been observed to contain substantial levels of huge variety of unrelated compounds, which are not associated with breath.The normal ranges of VOCs present in human breath are shown in table 2.

Common VOCs Present in Breath with Corresponding Diseases

Several numbers of VOCs present in exhaled breath can be recognized as probable biomarkers of various infectious diseases. The organization of specific disease to numerous types of biomarkers suggests that there might be some commonality to the effects of pathogenesis-related with different diseases (either different or unrelated diseases) that may result in similar alterations in biochemical pathways within the body [96]. In some cases, the pathogenic antigens that are most accountable for causing the diseased condition may be similar (such as toxins, enzymes, *etc.*), to create same biomarker metabolite sensuing in very comparable modes of action [97]. Table 3 presents major twenty five diseases with their specific VOCs as biomarker.

Breath Collection

Some techniques, for example, GC, require off-line breath collection and others can be used off-line if it is not possible to move the device to the subject or vice versa [130]. For sampling

Table 1: Physiological basis of VOCs production in human body.

VOCs	Physiologicalbasis	References
Hydrocarbon	Lipid peroxidation/metabolism	[52,72-74]
Carbon Monoxide	Heme catabolism	[38]
Ammonia, hydrogen sulphide, methylamine , methanethiol, methyl sulphide	Protein Metabolism	[47,75]
Methanol, ethanol, carbon disulphide, carbonyl sulphide	Gut bacterial metabolism	[76,77]
Aldehydes (acetaldehyde, formaldehyde)	Alcohol metabolism	[78-80]
Isoprene	Cholesterol biosynthesis	[81-83]

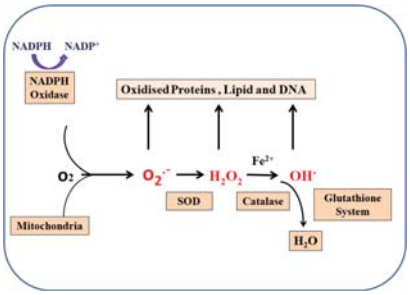
Table 2: Normal ranges of VOCs in human breath.

Group	Commonname	Conc. range (ppb)	Wt. avarge ppb(g/m^3)	References
Aldehyde	Acetaldehyde	3-7;ND-89.5	18(35)	[86]
	Formaldehyde	0.0003	0.0043(0.00528)	[87]
	Hexanal	9-13	11(45)	[86]
Ketone	Acetone	656-836	985(2330)	[86]
	Butanone	6-26	16(47)	[88]
	Methyl Ethyl Ketone	ND-45.3	10(29)	[89]
Alcohol	Isopropanol	50-260	150(370)	[136]
	Methanol	400-2000	330(430)	[90]
	Ethanol	1000	(1.40)	[88]
Hydrocarbon	Pentane	14	12(35)	[91]
	Ethylene	ND-223	23(26)	[89]
	Isoprene	70-580	210(590)	[88]
	Benzene	0.7-14.97	(4)	[92, 93]
	Toluene	1.45-37.21	(11)	[140]
	Napthalene	ND	(0.1)	[94]
	Xylenes	0.54-1.43	(0.2)	[139]
Ester	Ethyl Acetate	ND-116	17(62)	[89]
Others	Dimethyl Sulfide	ND-46.5	12(30)	[137]
	Furan	ND-78.4	14(39)	[137]

ND = Not Detected

Table 3: Some selective VOCs present in breath with corresponding diseases.

	Diseases/disorder	VOCs Detected	References
Cancer	1. Lung cancer	Methanol; isoprene; acetone;2-propanol(in all human breath); furan; acetonitrile; methyl furan (Smokers); alkanes.	[74,95]
	2. Breast cancer	1-phenylethnone; 2-propanol; isopropyl myristate; 2,3-dihydro-1-phenyl-4(1H) qunazolinone; heptanal.	[96,97]
	3. Stomach cancer	Carbon disulphide; acetone; ethyl acetone; ethyl acetate; 2-propanol.	[98]
	4. Colorectal cancer	Cyclohexene; 1,3-dimethylbenzene; 1,2-pentadiene, and methyl cyclohexene.	[99,100]
	5. Infection and tumor in Urinary headspace (prostate cancer).	Nitric acid; formaldehyde.	[101,102]
Liver Diseases	6. Liver diseases; fetor hepaticus	Methyl mercaptan; C2-C5 aliphatic acid.	[47,96]
	7. Liver cirrhosis	Carbon disulphide; acetone; dimethyl sulphide; 2-butanone; 2-pentanone.	[58,103]
	8. Hepatic coma	Methyl mercaptan; dimethyl sulphide.	[60]
Diabetes	9. Diabetes mellitus	Ethanol; acetone; methyl nitrate	[104]
	10. Diabetes	acetone; other ketones	[105,106]
Lung	11. Asthma	Pentane; NO; ethane; 8-isoprostane.	[60,107
	12. Emphysema	Isoprene; 2-methybutanal.	[108]
	13. Chronic obstructive pulmonary disease (COPD).	H_2O_2; NO; CO; alkenes; aldehydes; nitrotyrosine	[60,109,110]
	14. Cystic fibrosis	Carbonyl sulphide; alkanes; methyl thiocyanide; hydrogen cyanide.	[111]
	15. Active pulmonary tuberculosis	Cyclohexane; Oxetane; dodecane; benzene; decane; tridecane; heptanes and derivatives.	[63,112]
Metabolic disorder	16. Trimethylaminuria	Trimethylamine.	[113,114]
	17. Hypermethioninemia	Dimethyl sulphide.	[115,116]
	18. Tyrosinaemia	p-hydroxyphenylpyruvic acid.	[117]
Kidney	19. Uremia /kidney failure.	Dimethyl amine; trimethy amine.	[29]
Heart	20. Angina, ischemic heart disease	Alkanes; methylated alkanes.	[118,119]
Autoimmune disorder	21. Alograft rejection	Carbonyl sulphide.	[60,120]
	22. Rheumatoid arthritis	Pentane	[121]
Mental disorder	23. Schizophrenia	Carbon disulphide; pentane; ethane.	[122,123]
Others	Covid-19	Methanol, ethanol, octanal, acetone, butanone, isoprene, propanal, heptanal.	[124]
	24. Gynaecological tumours.	Volatile fatty acids.	[125]
	25. Cholera	Dimethyl disulphide; p-menth-1-en-8-ol.	[60,126]



ROS (Reactive O xygen Species)

ROS are the molecules or ions which are constantly produced in the mitochondria as part of the cellular respiration process. These molecules or ions have an unpaired electron in the outer shell and they may be produced by fungal and viral infections or they can stem from exogenous sources, such as cigarette smoke, pollution, and radiation.

Figure 1: Synthesis of Reactive Oxygen Species (ROS).

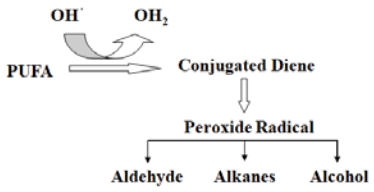


Figure 2: Free radical-mediated lipid peroxidation: possible reactions and reaction products.

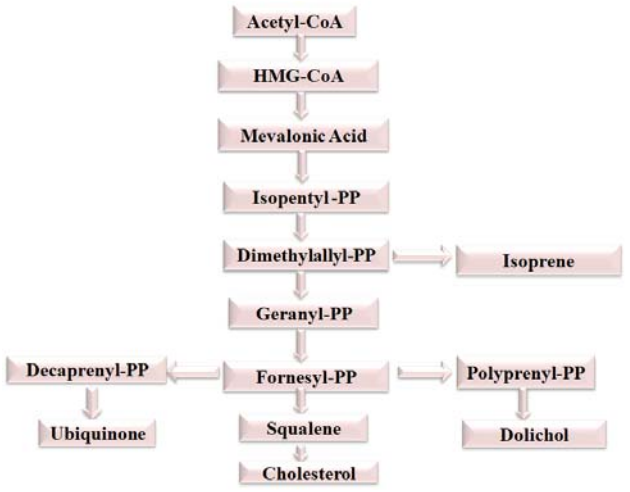


Figure 3: Cholesterol synthesis from Acetyl-coA and production of biomarkers through mevalonate pathway.

atmospheric gases and the headspace above blood samples and urine or cell cultures, the off-line collection is used [131]. Problems related to the off-line collection, storage, pre-concentration and consequent desorption are sample loss and contamination. A comparative study between off-line versus on-line breath HCN estimation in polymer bags reported higher analyte concentrations in on-line samples [16]; however, the variation may have been confounded by comparing mixed breath (off-line) and alveolar (online) samples [132].

Patients with fasting and without having smoked for 12 hours, the collection of breath occurred in the morning. Without using the toothpaste thepatients were asked to clean their mouth so as not to affect the measurement. Each subject was requested to breathe tidal volume for three minutes in a sampling device (Pneumopipe®, European Patent No. 12425057.2, Rome -Italy), through which the exhaled breath (tidal volume) was collected in an adsorbing cartridge (Tenax GR, the Supelco). The adsorbent cartridge solves the problems related to the use of the sampling bags: performing a stable concentration of the sample and facilitating the transport, also allowing the pre-concentration of the sample. The mouthpieces used for the sampling equipment were disposable.

Breathe Analysis Techniques

In the year of 1990s, analytical techniques were established particularly for breath analysis among which capillary Gas Chromatography (capGC) merged with Electron Impact Mass Spectrometry (EIMS) was widely used [133]. These occupy Proton Transfer- Reaction MS (PTR-MS), Selected Ion Flow Tube MS (SIFT-MS), Ion Mobility Spectrometry (IMS) and laser spectrometry. The laser spectrometry and direct mass spectrometric techniques even allowed the analysis of breath in real time, for example during the action of effort on an immobile bicycle, during sleep or in clinical settings. In competition, chromatographic techniques and related mass-spectrometric techniques became more superior. Two-

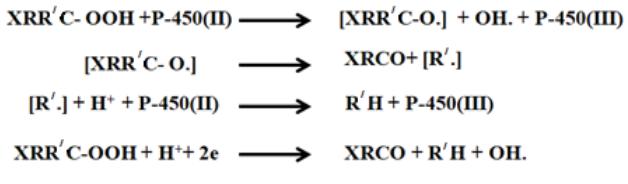


Figure 4: Scheme of aldehyde formation through reduction of hydroperoxide by cytochrome p450.

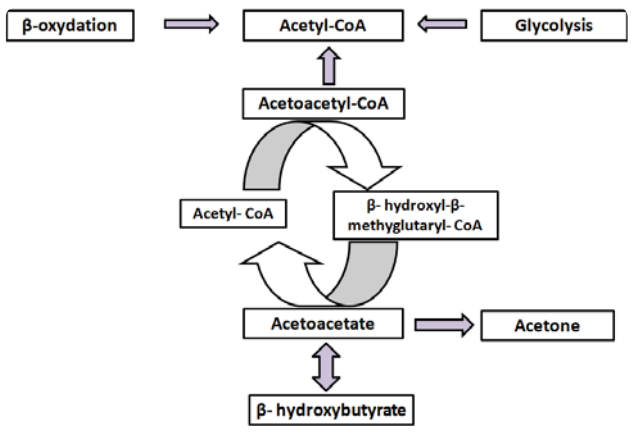


Figure 5: Generation of acetone in the liver by hepatocytes via decarboxylation of excess Acetyl-CoA.

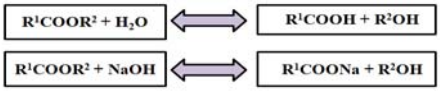


Figure 6: Hydrolysis of an ester under acidic conditions and alkaline conditions.

Table 4: VOCs sensing properties of some nanostructured metal oxide semiconductors.

VOCs	Material	Conc.(ppm)	Responce	Temp(°C)	References
Ethanol	SnO_2-core/ZnO-shell nanostructures	400	128c	400	[162]
	WO_3–(0.54)SnO_2	180-2800	392-1476	300	[163]
	Ce –SnO_2NPs	200	185b	250	[164]
	In_2O_3NFs	15000	3790c	300	[165]
	Flower-like ZnO NRs	50	119b	400	[166]
	TiO2 nanotubes	1000	1380000d	250	[167]
Acetone	α -Fe_2O_3@ZnO coreshell	100	280b	12	[168]
	Pd-WO_3nanorods	200	138.62a	300	[169]
	Au-WO_3nanorods	200	131.26a	300	[169]
	AuPd-WO_3nanorods	200	152.4a	300	[169]
	SnO_2	1000-4000	40-80	350	[261]
Formaldehyde	10 mol% CdO-2.2 mol% Sn doped ZnO	200	2000b	200	[170]
	Nano ZnO	1000	997b	210	[171]
	Cd activated Sn-ZnO	1-205	10	200	[172]
	CdO–In_2O_3	10	100b	95	[173]
	In_2O_3/ZnO	100-2000	0.3	300°C	[174]
	Mesoporous wormlike SnO_2NPs	10	100b	150	[175]
Toluene	MnO-Indium Tin Oxide (In_2O_3:10% SnO_2) thin films	1000	85b	227	[176]
	Ni doped ZnO	5	25a	400	[177]
	Mesoporous Co_3O_4	100	23.55a	190	[175]
	SnO_2-Fe_2O_3 nanotubes	50	25.3a	260	[178]
	TiO_2nanotubular	500	53a	500	[179]
Methanol	La1-xMgxFeO_3	100	150a	190	[180]
	CdS-doped SnO2 thick films	5000	70a	200	[181]
	3 wt.%PbO doped SnO_2	1000	69.5b	350	[182]
	La0.8Pb0.2FeO3 NPs	200	50b	230	[183]
Acetylene	Pt loaded ZnO	10000	836a	300	[184]
	6% wt Sn_2O_3-doped SnO_2	1000	65a	180	[185]
Benzene	Cr/ ITO thin film	1000	72b	210	[186]
	ZnO–TiO_2	100	27a	370	[187]
	Mesoporous wormlike SnO_2NPs	10	20a	150	[175]

Here the subscript denote- a: (Ra/Rg, %), b: (Ra/Rg or Rg/Ra), c: ([Ra-Rg]/Ra, %), d: ([Ia-Ig]/Ia).

dimensional gas chromatography (GC×GC) in mixture with fast mass spectrometric detectors such as Time-of-Flight (TOF) were established and applied to a breath analysis. These new techniques permitted the separation of breath into hundreds of compounds. Additionally, short multi-capillary columns (MCC, with relatively short retention times of 1 min) might be attached to an IMS or to a PTR-TOF-MS. These novel techniques have a time resolution of 1 min.

To progress in the identification and quantification of trace gases in breath, several techniques are now in use having their own advantages and disadvantages which describes in following section (Sec 6.1 to 6.12.). Although only a few of them can accurately quantify VOCs at the low ppb level, online and in real time.

Gas chromatography

Gas chromatography (GC) is the most typical technique for the study of volatile compounds in breath research [134]. Whereas mixtures of compounds are separated through their reaction with the substance of the GC column [135]. When the GC worked with Flame Ionization Detection (FID), Mass Spectrometry (GC-MS)

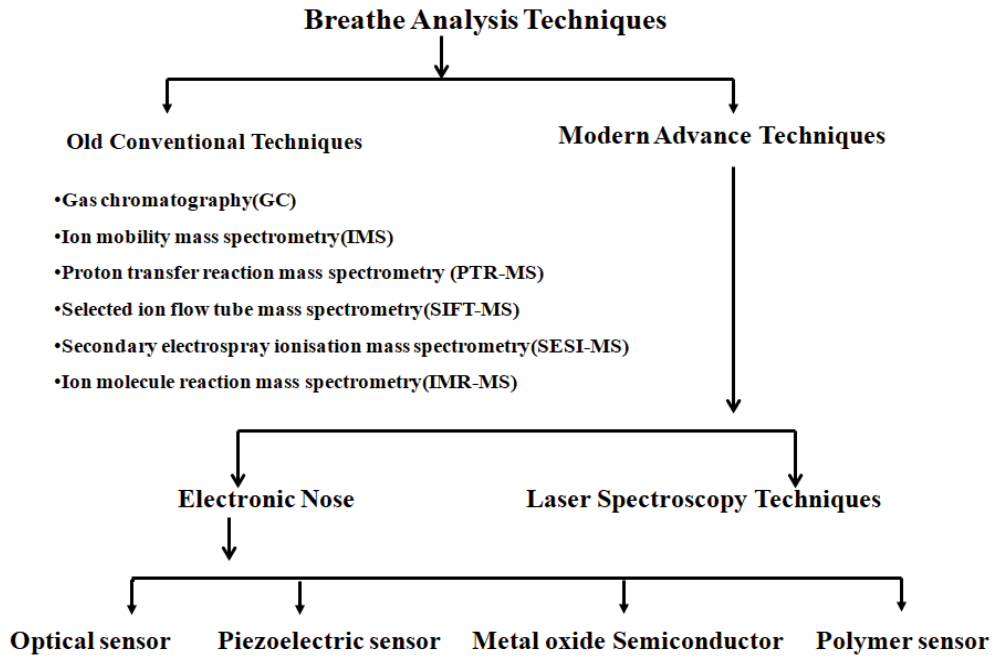


Figure 7: Different techniques used in breath analysis.

[136], and Time-of-Flight (TOF) provides scientists a huge quantity of information regarding the composition and identification of compounds of the sample which gives information regarding the biochemical processes of the body. The breath sample contains enormous amounts of compounds and the disintegration of the compounds by GC-MS instruments produces mass spectrometric fingerprints which can be searched by means of spectral libraries, like National Institute of Standards and Technology (NIST), to discover the detected compounds. Demerits of GC-MS instruments for breath investigation viz.

a) areas of standarisation

b) accuracy of identification of the compounds of very low molecular weight

c) collection of materials and

d) this procedure is time-consuming and requires trained operator owing to the sample preparation steps and raw results data.

Ion mobility spectrometry

This analytical technique is designed to separate and identify ionized gas molecules in accordance to their mobility within the carrier buffer gas. This method is especially used to detect drugs and explosives for security purpose and also has lots of applications that include the consideration of this device come in various sizes, and is capable of operating broad range of condition depending upon specific application. IMS can be used nicely to detect and quantify trace gases as ppb level [137]. Ionization of sample to be needed in this technique, usually done by photoionization, electronspray, corona discharge or radioactive sources into a drift tube. A mass spectrum is produced when product ions with various molecular masses appear at the detector at various times due to their different drift velocities. By changing the drift length, drift gas, electrical field strength, temperature or pressure, product ion separation can be improved. This method is highly sensitive to facilitate separation of complex gas mixture coupled with GC, MS or LC but calibration of ion mobility for each ion species at different humidity level is necessary due to time consuming.

Mass spectrometry: proton transfer reaction and selected ion flow tube

Proton-Transfer-Reaction Mass Spectroscopy (PTR-MS) [138] and Selected-Ion Flow-Tube Mass Spectroscopy (SITF-MS) [138] are used for online monitoring of VOCs at very low concentration and mixed sample. Both methods are fast, handyand determine the breath samples without any pre-concentration over a wide range of temperature. The sizes of both instruments are very large, although commercially in recent decades companies keep trying to reduce the size of the instruments. The functional time of PTR-MS and SIFT-MS instruments are near about 100 ms and 20 ms respectively. In the case of PTR-MS technique, hydronium (H_3O^+) reagent is used in the gas phase, whereas in SIFT-MS, anyone of H_3O^+, NO^+ and O_2^+ are used as precursor ions. The chemical ionization technique is applied for the determination of a small number of volatile compounds. Since consumables are low in cost and sample preparation is not required, the analysis of breath samples is also inexpensive if the instrument is purchased once. The precursor ions of the particular instrument react with the VOC components to produce the complex ions and the air is act herein as the buffer gas. In a computer database, the complex ions are detected with their mass-to-charge ratios (m/z) [140] which are already standardized. Drawback of the PTR-MS instrument is that it cannot identify the isobaric product. Therefore another method is required for complex ion analysis.

Secondary electrospray ionisation mass spectrometry

Secondary electrospray ionisation (SESI) [141-143] was established to separate the ionization of species originally within

a gas external in addition to the sprayed liquid from traditional Electronspray Ionization (ESI) associated with an analyte originally dissolved inside the sprayed liquid. This method involves passing a gaseous sample in a stream of air or CO_2 through a cloud of electro spray solution with which the volatile analytes react to become protonated. Product ions are driven by an electrical field and are sucked into the inlet of the triple quadruple mass spectrometer for detection and analysis. Analytes within the gaseous phase and those condensed in water droplets can be ionised by this technique. Secondary Electronspray Ionization Mass Spectrometry (SESI-MS) which happens to be the most appropriate for detecting VOCs with no need of sample preparation. Excellent sensitivity, due to the low parts per trillion (ppt), is possible over a prolific number of masses (over 600 Da), with results of a complete mass scan is supplied in less than 2 min. Unlike PTR-MS and SIFT-MS, the fragmentation of compounds of great interest by SESI enables exact compound identification by MS.

Ion molecule reaction mass spectrometry

Another breath analysis technique briefly described here is Ion-Molecule Reaction MS (IMR-MS) [144], which has been effectively used for the diagnosis of liver disease. According to Millonig, et al. [145], this system provides a highly sensitive analysis for online and offline sampling of organic and inorganic compounds in exhaled breath. This type of ionization can be used for the identification of different molecules of the same molecular weight, for example, acetaldehyde or carbon dioxide, and undoubtedly there is a huge benefit of this method of excitation.

Optical spectroscopy

Optical spectroscopy displays a very powerful technique for analysis of exhaled breath VOCs and also for other small gas molecules. This technique might be used to identify and quantify a single substance in the breath, online and in real time that does not require an expert user [146]. Among the other online analytical methods utilized in exhaled breathe VOCs, optical spectroscopy lies in between mass spectrometers and sensors. One example of this type of instrument is the chemiluminescent analyzer for measuring FENO [147], which measures light produced by the reaction of NO in the airway with ozone. Currently, optical instruments usually are not helpful for specific target of exploratory biomarker, but when using the rapid making of OFC spectroscopy, this will likely change within the near future.

Electronic Nose (e-nose)

The electronic nose (e-nose) simulate olfactory system of the human body [148], which allows detection of various volatile compounds or odours. The human nose consists of a large number of olfactory receptors [149], which generate electrical signals as a result of specific interaction with the respective odour receptors [150]. A single neuron corresponds to different odours, and the interaction of many neurons serves to identify and classify smells [151,152]. The initiative of imitating the olfactory method has been used in pursuits to build an *e*-nose [148]. As in the olfactory method, the scent recognition by an *e*-nose is concluded through the use of selective electronic sensors. The quantity of sensors is increasing with the progress of electronic technology. Selective sensors used in *e*-noses are mainly optical sensors, piezoelectric sensors, metal oxide semiconductors and conducting film polymers.

Optical sensor

Optical Sensors (OS) are extensively used in several fields of science [153] because the data output can be precisely measured and defined. For detection of exhaled breath VOCs optical sensor have been used [154]. Although the OS is typically more complex than other sensors, they provide different measurement possibilities. Additionally, the electromagnetic radiation interact with matter occurs in a broad frequency range. The manufacture of major parts of the OS is a light source, optical elements (lenses, mirror, prisms, diffraction gratings, etc.) and detectors. The interaction between the light source (often LED) and volatile molecules results in effects that can be measured by absorbance [155], reflectance and refractive index investigation. Other effects regarding colourimetric signalsor chemiluminescencehave also been observed [156].

The most direct way is to measure the absorbance of the detected analyte in a specific frequency range. Detection of gases such as hydrogen, oxygen or hydrocarbons is one of many good examples. However, the method is not sensitive in recognition of other compounds at low concentrations. A simpler solution is to measure the colour change of a marker such as metalloporphyrins. A thin-film layer consist of dye molecules is used as the sensitive marker in colourimetric sensors [157]. Dye colour changes as a result of the impact of chemical molecules on the film, and the RGB (red, green and blue) value of the colour is evaluated by computer software.

Piezoelectric sensor

Interaction of some sensors with the relevant analytes can lead to mass changes [158]. This phenomenon was termed the piezoelectric effect [159]. The use of a piezoelectric crystal initiated the development of a microbalance mass sensor. In such devices the signal is generated by the adsorption of the analyte molecules to the sensor surface [160]. The selectivity and sensitivity of Quartz Crystal Microbalance (QCM) dependent on receptor surface coverage [161], in addition to its width and process of deposition. The main advantages of mass sensors are a simple design, small size and low power input [162].

To identify amines and acetaldehyde, piezoelectric sensors have been used [163]. Using eight QCMs of diabetic patients in breath Fleischer et al. proposed to measure acetone concentration. Quartz microbalance can be applied to examine the concentrations of butyric acid, valeric acid and hydrogen sulfide in exhaled breath. These three compounds are identified as biomarkers of halitosis. Pennazza proposed a prototype *e*-nose consisting of seven quartz microbalances. The surface of each microbalance was layered with other metalloporphyrin complexes of the following metals: cobalt, copper, zinc, iron, manganese, chromium and tin.

Metal oxide semiconductors

Metal oxide semiconductors (MOS) are another example of sensor systems used to detect important breath gases (CO and NOx) [164,165]. NOx is an important indicator for analysis of asthma and its therapy control. The receptor layer of these sensors is made up of metal oxides. The metal oxides e.g. WO_3, ZnO, TiO_2, CuO and In_2O_3 are used as a selective recognition of VOCs [164,166]. The conductivity of oxide on the semiconductor surface changes due to the presence of VOCs as a consequence of a redox reaction [167,168]. The presence of reducing gases such as hydrogen or hydrocarbons reduces the density of oxygen atoms, leading to an increase in conductivity [162]. Conversely, increasing oxygen concentration in

a gas mixture causes the reduction in conductivity. The selectivity of MOS can be resolved by metal oxide electronic structure [169]. There are two groups of electronic structures: transition-metal oxides and non-transition metal oxides.

The most important parameters of MOS that are accountable for conductivity change are surface-modification and microstructures of receptor layers, temperature, reduction reactions, and humidity [170]. In metal oxides, the resistance in the air is due to the control of surface reactions as well as electron replace between the metal oxide and chemisorbed oxygen species. Oxygen species from air environment accumulate on the semiconductor metal oxide particles surface in the ionic forms as O^- (ads) and O^{2-} (ads). However, chemisorptions are an energy activated processes and each oxygen species requires different temperature to take place on the surface of the grain. The O^{2-} (ads), requiring high activation energy to be chemisorbed, is normally presented at higher temperatures whereas the other ones are the plausible ionic species at lower temperatures. Particularly, at less than 400 °C temperatures almost all of the metal oxide based VOCs sensors work where the O– (ads) is the predominant species.

The mechanism of the gas sensor is essentially explained by the energy-band bending theory. When O_2 molecules accumulate on the metal oxides surface, they would remove electrons from the conduction band by trapping charges at the surface of grain in the ionic form. From a practical viewpoint, it is likely to believe that the delocalization of electrons from the bulk of the grains to their surface resulting in the formation of holes in the bulk and an adsorption of negative charge on the surface. This generates the formation of an electron depleted region, called space-charge layer, then in an energy-band bending. Between grains, the combination of the two weakening regions brings about an energetic boundary known as a Schottky barrier, the magnitude of which depends on the conductivity of the material. With the help of the reaction between adsorbed VOCs and oxygen species can adjust the intensity of the Schottky barrier, resulting in a conductivity variation. Because the amount of energy level is directly linked with the number of molecules reacting with the metal oxide surface, the difference of electrical parameter of the sensor (i.e. resistance, current) could be used as variable to monitor the concentration of VOCs species.

The identification of VOCs such as acetone, ethanol, formaldehyde, methanol, benzene, toluene etc. by means of sensors based on metal oxides has been widely studied over the recent years. Usually, it has been shown that some metal oxides with various structures are able to identify VOCs at concentrations ranging parts per million with more or less significant performance. Table-3 shows the VOCs sensor properties of some metal oxide semiconductor nanostructures. Among them, SnO_2, ZnO, WO_3, TiO_2, In_2O_3, Co_3O_4 based nanostructures show the most hopeful sensing performance for the monitoring of VOCs.

Polymer sensors

Polymer surfaces are another example of sensors used in electronic noses [197]. Volatile compounds, gases and odours selectively adsorbed on the surface result in a change of conductivity that can be monitored [198]. The number of polymers that are suitable for breath molecule detection is systematically rising, mostly through several modifications [199]. Polypyrrole, polyindol, polyfuran, polyaniline, and polythiophene are the most accepted conducting organic polymers [200], while have been used to identify exhaled volatile molecules of air. To identify volatile compounds, Silva *et al.* tested a responsive film of poly (methyl [3, 3, 3-trifluoropropyl] siloxane) [201]. Dragonieri, et al. [202] reported malignant pleural mesothelioma indicators by using a commercial electronic nose (Cyranose 320) which consist of 32 dissimilar polymer sensors. Kukla, et al. suggested the use of three polymer films (polypyrrole, polyaniline, and poly-3-methylthiophene) for the investigation of nine VOCs(203). Major advantages of using an *e*-nose are inexpensive, rapid analysis, easiness of use and miniaturization of the equipment. However, this method has a considerable drawback: to be successfully used, the electronic nose has to be trained on a group of patients to identify the specific odor/biomarkers to create, for example, the cancer prediction model, and then on a second group to validate the model.

Laser spectroscopy technique

Laser absorption spectroscopy is based on interaction between light and the medium [204]. The absorption level is determined by measurement of radiation attenuation passing through the medium. This attenuation is described as a decrease in radiation power registered by a detector. There are also other identification techniques using various light-material interactions that causes acoustic wave generation and modulation, temperature changes, generation of the electric current (optogalvanic spectroscopy), and so on.

VOCS PRESENT IN SOME COMMON DISEASES: A SYSTEMATIC STUDY

A thorough comprehensive study of most common diseases, as listed in Table 3 and their corresponding biomarkers reveals the scientific basis of metabolic state and the related VOCs in different diseased states.

Lung cancer

With the lowest survival outcomes, Lung Cancer (LC) is the most familiar of any cancer because over 68% patients are diagnosed at last stage when therapeutic treatment is not possible [205]. Major causes of lung cancer are long term tobacco smoking, exposure to radon gas, asbestos, passive smoking or other forms of air pollution and genetic factors [206, 207]. In a cross sectional study, Phillips and co-workers (1999) suggested a mixture of twenty two VOCs as possible biomarkers in breath sample of patients with lung cancer [74]. Principally alkanes (such as hexane and methyl pentane) and benzene derivatives (e.g. O-toluidene, aniline) are found in the breath of LC patients [208].

In order to recognize the VOCs in breath of LC patients, predominantly Gas Chromatography–Mass Spectrometry (GC-MS) [209-212] and Proton Transfer Reaction Mass Spectrometry (PTR-MS) [213-215] have been executed and several types of VOCs have been recognized in human breath. Classic examples include acetone, methanol, isoprene, furan, 2-propanol, limonene, acetonitrile, 2-methyl furan, hydrogen, methane, or ethane and pentane [98]. Despite the promising advances, the lack of standardization and normalization has led to huge alterations in the VOC profiles [216].

Breast cancer

One of the leading type of cancer in women which accounts 25% of all cases and is more than hundred times more common in women than in men is Breast Cancer (BC) [217,218]. Major risk factors for increasing BC in female are lack of physical exercise, obesity,

hormone replacement therapy during menopause, etc. [219-222]. By analyzing breathe of the women with BC Hietanen and coworkers identified increased concentrations of pentane by an initial case control study [131,223]. A pilot study of breath VOCs in women with BC was performed by Phillips and co-workers. After investigation of breath samples by GC-MS, compared with biopsies and abnormal mammog rams, they found the breath test could distinguish between healthy volunteers and a women with BC with a sensitivity of 94.1% [224]. Though their findings were reliable with different studies, the biochemical origin of breast cancer biomarkers remains speculative [131].

Liver diseases

There are more than a hundred types of Liver Diseases (LD) [225] caused by different types of factors – such as genetic, viruses, alcohol consumption, obesity, etc. [226]. Van den Velde and co-workers recognized twelve types of VOCs considerably different from healthy and cirrhotic subjects by analyzing the breath of 50 cirrhotic patients [227]. VOCs such asdimethyl sulfide, hydrogen sulphide, and mercaptans (e.g., methyl mercaptan and ethyl mercaptan) are anticipated as liver cancer biomarkers [228]. When the liver is unable to transfer ammonia to urea, ammonia levels rise in the blood and this may occur because of cirrhosis or severe hepatitis; however, ammonia exposure in mouth-exhaled breath occurs due to creation of ammonia in the oral cavity. Poor oral hygiene can be a confusing factor, because conversion of urea to ammonia may increase the concentration of ammonia in exhaled breath [229,230]. Such a situation can be overcome by washing mouth thoroughly with water before breath sampling. Hepatic encephalopathy is a neuropsychiatric syndrome [231,232] with changing symptoms depending on the strictness of the condition. Ammonia is known to be involved in hepatic encephalopathy [233]; however, attempts to use measurements for diagnosis of breath ammonia have failed. Insufficient information and some confusing factors have proven to be difficult in VOCs detection and quantification of LD [234].

Colorectal Cancer

Genetic predisposition and environmental factors, including lifestyle and diet are the contributing factors for Colorectal Cancer (CC) [235]. Within lifestyle factors, elevated Body Mass Index (BMI), obesity, and low physical activity are related to increased risk of CC [236-240]. The findings indicated that diets low in fat and rich in protein-induced systemic ketosis leading to increased levels of acetone in breathe [241,242]. Acetone may appear in the breath and may be converted to isopropanol by hepatic alcohol dehydrogenase [18]. Carbohydrate fermentation by bacteria in the gut results in the production of carbon dioxide, methane, hydrogen, and Short Chain Fatty Acids (SCFAs) mainly propionate, acetate, and butyrate as the final products of fermentation. Early measurements of breath hydrogen have been used to study carbohydrate absorption in the small intestine [243]. Correspondingly, assessments of methane in breath have been used to measure the bacterial metabolism of the colon [244,245]. Short chain fatty acids are assimilated by the host and used for the energy metabolism [246]. Butyrate has been measured to detect the defensive role against colitis and colorectal cancer [247]. According to Schmidt and co-workers with the intake of food or drink the concentration of hydrogen cyanide in breath maybe increased [131]. Ammonia, isobutyric acid, hydrogen sulphide, phenolics and isovaleric are the molecules which have been identified as products of gastrointestinal bacterial fermentation.

Recently, Altomare and co-workers examined breath samples of CC patients using GC–MS and found that the concentration levels of some specific VOCs such ascyclohexene, 1, 3-dimethylbenzene, 1, 2-pentadiene, and methyl cyclohexene were significantly different from the pattern of VOCs in healthy controls [248]. However, to support this experiment advance studies are needed.

Tuberculosis

Pulmonary Tuberculosis (TB) is the second biggest killer globally. In 2015, total 10.4 million TB cases were enumerated around the world among which lethality was 1.8 million. Now TB is one of the top three causes of death for women aged 15 to 44. It is a transmittable disease caused bymicroorganism Mycobacterium tuberculosis [249,250]. Active infection occurs more often in people with HIV/AIDS and those who smoke. The primary detection technique is the Ziehl-Neelsen staining [251,252] combined with microscopy. It only allows recognition of pulmonary disease in an early stage, meaning that often the disease has already been transmitted to close contacts. Breath analysismay be usedas good technique for diagnosing tuberculosis. Some compounds such as methyl *p*-anisate, methyl nicotinate methyl phenylacetate and *o*-phenylanisole have been found by breath sampling as potential biomarkers of tuberculosis [253,254]. This means that if VOCs are produced, they may be released or mitigated by the host; hence, they may be present at low concentration and can be recognized by the real-time analytical techniques.

Diabetes Mellitus

Diabetes Mellitus (DM) or commonly known as diabetes, is a group of metabolic disorders that causes high blood sugar levels over anelongated period [255]. Among the three main types of diabetes major is of type-1(T1DM) but causes of T1DM are still unknown though other types are caused by obesity, stress, lack of exercise and genetic factors [256]. Twenty years from now, type-1 (T1DM) and Type-2 Diabetes Mellitus (T2DM) are projected to affect nearly 450 million people worldwide [257]. Normal diagnosis and management of this disease is based on blood test which may be expensive, impractical and even painful. Huge resources have been invested worldwide for the developing of non-invasive devices fordiabetes detection, butimprovement has been slow. However, no FDA (Food and Drug Administration) permitted products are commercially available till now though some devices for non-invasive blood glucose testing were readily available in market [258]. Yet there is no existence of any Real-time insulin or lipid meters. Among a lot of non-invasive testing for diabetes management, breath based devices have many advantages [259]. Breath analysis is gladly acceptable by patients while collection of breath is easy and can even be obtained from unconscious and neonatal patients. The highly soluble gas acetone is most frequent metabolite present in exhaled breathes [260]. Results have shown that the acetone concentrations in exhaled breath is increased after intake of a ketogenic meal, or following a low carbohydrate diet [242]. Smith and co-workers described that for the period of fasting a change takes place from carbohydrate to fat metabolism when the concentration of breathe acetone increases significantly [131]. Using PTR–MS, recently it was found that the concentration of breathe acetone may differ with fasting state and age, but no statistically key differences between gender and Body-Mass Index (BMI) were found (Schwarz and co-workers) [19]. Another study executed in healthy and type-1 diabetic patient showed a very strong connection with concentrations of glucose and compounds present in exhaled breath. On the other hand, for type-2 diabetes slight is presently known.

Some measurements of breath acetone in type-2 diabetes were taken without any considerable results. By portable gas sensors and PTR-MS equipped with a time-of-flight mass analyzer, Righettoni and co-workers conducted a study and concluded the interconnection between blood glucose of healthy volunteers and breath components [261]. They also studied the relationship between breath gases such as ethanol, acetone, methanol, and isoprene, sensor response and the blood glucose level. They examined a better correlation between breathe acetone and blood glucose levels for the overnight fasting (morning).

Asthma

A common chronic inflammatory disease of the airways of the lungs is Asthma. According to WHO near about 235 million people currently suffer from asthma and is most common disease among children though lethality is predominant in the older people [262]. It is characterized by reversible airflow obstruction bronchospasm [263]. Asthma is caused by a combination of environmental and genetic factors, whereas it is classified as allergic and non allergic. VOCs in exhaled breath samples can discriminate asthmatic from healthy children and atopics from non-atopics with a relatively high sensitivity and specificity and limited intra-individual variability [264]. From different studies of exhaled breath, a combination of 6 VOCs was able to predict irritation in asthmatic children [265]. Collection of VOCs is also feasible in preschool children, and it was shown that VOC profiles differ between children with and without recurrent wheeze [266,267]. Overall, the best discriminating VOCs for asthma are nitric oxide, pentane, ethane, and 8-isoprostane, etc [268]. However, each individual study demonstrates a different superior set of VOCs, and there is clearly a need for external validation. Therefore, further research is also required on VOCs in children with asthma. Hence, VOCs in exhaled breath may be helpful for asthma diagnosis, but their role in asthma monitoring is still unclear.

Schizophrenia

Schizophrenia is a common and overwhelming psychotic illness characterized by abnormal behaviour, strange speech, and a decrease ability to understand reality [269]. It affects nearly 1% of the population globally and often ends with severe abnormality and early deaths. The aetiology of schizophrenia is still unknown and researchers have used various types of analytical techniques to establish a biochemical basis for the disordered perception and behaviour that specify the disease [270]. Though specialists believe a number of factors are usually involved in contributing to the on-set of schizophrenia, evidences suggest that environmental and genetic factors act together to bring about schizophrenia [271,272]. Though diagnosis of schizophrenia is very difficult but recent studies of breath analysis of schizophrenic subjects shows very good techniques for diagnosis of this disease. Kovaleva et al. [125] investigated the breath of severely psychotic schizophrenic subjects and found increased concentrations of pentane which differs with the clinical cruelty of the condition. Microanalysis combined with pattern recognition analysis of the VOCs in the alveolar breath identified schizophrenia patients with a sensitivity of 80% and a specificity of 61.9% [126]. Different studies of breath analysis identified alkanes (mainly pentane and ethane) and carbon disulphide as a potential biomarker of patients with schizophrenia [273].

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease, characterized by long term breathing problems and poor airflow due to oxidative stress and the formation of VOCs secreted *via* lungs [274, 275]. In developed countries, the main causes of COPD are tobacco smoking [276,277]. On the other hand in developing world, COPD occurs in people exposed to fumes from burning fuel for cooking and heating in poorly ventilated homes [278]. Therefore, improvement and innovation of tools determining airway inflammation are required in the pathogenesis of COPD. Direct estimation of airway inflammation requires invasive procedures though there are limitations too. Hence, non-invasive approach has great prospects to sampling airway inflammation. Analysis of Exhaled Breath Condensate (EBC) is rapidly growing up as a non-invasive approach for sampling airway epithelial lining fluid and provides biomarkers of inflammation. Three VOCs such asphenol, indole, and hexanal have been recognized as biomarkers of COPD in more than one research findings [279]. It is reported that phenol is exclusively recognized by GC-MS and measured as a usual metabolite of cyclohexanone and benzene, which are also identified as pollutants. Both of these VOCs were also reported as potential markers of COPD [280]. However, phenol has been identified as a tyrosine metabolite in the intestine by gut flora [281], and it was also recognized in the urine analysis of other diseases as well.

The increase of non-endogenous VOCs may be related to smoking or air pollution, and both are the hazard for COPD. In addition to phenol, hexanal was identified by more than one study. Hexanal can be used as a biomarker for lipid oxidation, and also utilized for estimation of lipid oxidationin vitro [282]. In the human body indole is generated from metabolism of tryptophan amino acid through the enzyme tryptophanase by gut flora. Metabolism of tryptophan has been interrelated with COPD through moderate levels of indoleamine 2, 3-dioxygenase in humans [283]. However, this pathway does not produce indole but is considered as the kynurenine pathway [284].

COVID-19

Recently, a severe and highly contagious viral disease was evolved in Wuhan, China. The causative agent was detected to be a new coronavirus and termed as Coronavirus disease 2019 (COVID-19) [285,286]. The virus spread rapidly around the world, and the World Health Organization (WHO) declared a pandemic in March 2020. The coronavirus has been responsible for 120 millions of cases globally, and it has caused more than 2.6 million deaths and affected more than 210 countries and territories worldwide. SARS-CoV-2 can spread with human-to-human transmission via respiratory droplets viz. through coughing or sneezing [287,288]. Patients develop symptoms of covid-19 after some days of exposure, causing late diagnosis and high infection rate [289-291]. To diagnosis of novel corona virus (COVID-19) RT-PCR (reverse transcription polymerase chain reaction) test is available and the test involves taking nasal and throat swabs [292]. During the process of diagnosis time required for sampling and analysis is too long. The sample may contain too little virus because of the location swabbed is not appropriate for the stage of infection. Hence this may lead to a high rate of false negatives and thus repeat testing or further test being needed for reliable results. In this point of view breath analysis will be suitable techniques for the diagnosis of covid-19. Breath analysis is already being used for the analysis of biomarkers for novel corona virus detection. D. M. Ruszkiewcz, et al. [293] have found mainly six VOCs by analysis of breath with GC-IMS are ethanol, octanal, acetone, acetone/butanone mixed cluster and methanol. They have

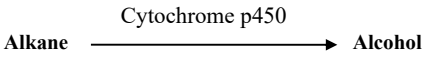
found exhaled methanol concentration lower in covid-19 patients whereas other five compounds were elevated in covid-19 patients. Recently another noninvasive approach, using nanomaterial based sensor array for detection of covid-19 in exhaled breath done by B. Shan, et al. [294] and has a potential ability to serve as an epidemic control tool. Though there is needed much more research for breath based techniques to detect covid-19 disease, but it may already great promising approach in future.

IOCHEMICAL SYNTHESIS OF VOCS PRODUCTION IN HUMAN BODY

Biomarkers are produced through different biochemical pathways. On the basis of cell biology, various numbers of VOCs are generated by different biochemical processes, such as metabolic disorders. Since liver enzymes can cause an effect on the cell membranes, which mainly consist of amphipathic phospholipids, carbohydrates and many integral membrane proteins.

Hydrocarbon

The emission of hydrocarbons in our body is one of the mechanistic pathway for oxidative stress. Generally, alkanes are produced from Polyunsaturated Fatty Acids (PUFA) by lipid peroxidation through Reactive Oxygen Species (ROS) [282,295]. Pentane or ethane has been extensively used as a sensitive and non-invasive indicator of lipid peroxidation [296]. Due to absence of polyunsaturated fatty acids in the body, Kneepkens et al. claimed that branched hydrocarbons are not produced from lipid peroxidation [98]. Whereasin human breath, isoprene is produced in the cytoplasm fraction by the mevalonate pathway of cholesterol synthesis [297].



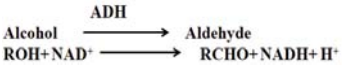
Due to their lesser solubility in the blood, the hydrocarbons are excreted into the breath within minutes.

Mevalonate pathways of cholesterol synthesis and production of biomarkers

An important reaction in the cholesterol biosynthesis is the formation of mevalonate (HMG)–CoA. In the cytosol, mevalonate is transformed to isopentenyl pyrophosphate, which further isomerises to Dimethylallyl Pyrophosphate (DMPP). This DMPP is rapidly changed into isoprene followed by acid-catalyzed pathway via the formation of carbonium ion.Certain plants may also produce isoprene from DMPP in which the reaction is catalyzed by Mg^{2+}-containing enzyme.In mammalian tissue, sterol synthesis is catalyzed by hydroxymethylglutaryl. This enzyme may be the Mg^{2+}-dependentisopentenyl and DMPP. This isomerisation reaction travels through pyrophosphate isomerises, which catalyzesthe inter-conversion of isopentenyl pyrophosphate, as happens in the acid-catalyzed non-enzymatic conversion of DMPP to isoprene. In humans, the parallel diminish in sterol synthesis and isoprene secretion triggered by severe or chronic lovastatin administration suggests that breath isoprene is produced from the pathway of cholesterol synthesis in vivo. A little portion of exhaled isoprene perhapsoriginates from bacteria. The experimental evidence of isoprene exhalation perhaps is related to oxidative damage to the fluid inside the layer of the lungand the body. Unexpectedly, laboratory animal's breath isoprene concentrations are significantly lower than in the exhaled breath of a human.

Alcohols

Most of the alcohols are produced from food and alcoholic beverages and the metabolism ofhydrocarbons [298]. Since alcohols have higher affinity towards water, it is readily absorbed in the blood and found in the body tissue. Therefore a small amount of alcohols may appear in the breath of people who have not taken alcoholic beverages at the time of the breath test. In liver alcohols are metabolized into aldehydes by various types of enzymes, such as Alcohol Dehydrogenase (ADH) and cytochrome p450 (CYP2E1) [299].

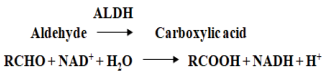


Alcohol dehydrogenase (ADH):

A member of the general class of enzymes that happens in many organisms and promote the inter-conversion between alcohols and aldehyde or ketones with the reduction of nictotinamide adenine dinucleotide (NAD^+ to NADH) mainly in the liver. ADH can catalyse the oxidation of many different alcohols in humans, including primary, secondary cyclic secondary hemiacetal.

Aldehydes

Aldehydes are produced throughcommonphysiological processes and biotransformation events [300]. Some portions of aldehydes are involved in various functions via cytotoxic intermediates, such as cellular proliferation, gene regulation, and signal transduction. There are several sources of aldehydes in the body. First source is metabolism of alcohol. For example, acetaldehyde and formaldehyde are produced from ethanol and methanol respectively by alcohol dehydrogenase [301]. Furthermore, aldehydes, are oxidized to carboxylic acids by the enzyme Aldehyde Dehydrogenase (ALDH) [302]:



Aldehyde dehydrogenase (ALDH):

Aldehyde dehydrogenases are a group of enzymes that catalyses the oxidation of aldehyde s. Although they are called dehydrogenases, they actually add an oxygen atom to the aldehyde rather than take away hydrogen atoms. To date, nineteen ALDH genes have been identified within the human genome. These genes participate in a wide variety of biological processes including the detoxification of exogenously and endogenously generated aldehydes.

On the other hand, aldehydes may alsobe producedby the reduction of hydroperoxide by cytochrome p450. In the first step of hydroperoxide reduction produces alkoxy radical by a step wise one electron. Then this alkoxy radical undergoes the β-scission reaction to producean aldehyde or a ketone and a radical, R•.

The third resource of aldehydes is associated with cigarettes. In tobacco smoke aldehydes remain in both saturated (acetaldehyde, formaldehyde, propionaldehyde and butyraldehyde) and unsaturated (crotonaldehyde and acrolein) forms [303].

Finally, aldehydes are produced in the body as a byproduct of tobacco metabolism by cytochrome p450 [282]. This process generates an additional oxygen atom to the foreign compound and thus creates a more water-soluble substance. It means, the process transformsthe hydrophobic carcinogens into a form that is easier to remove from the body. One of the example of such process is the metabolism of a carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is converted to α-hydroxy-NNKs by cytochrome p450 enzymes and it readily degradesinto aldehydes and diazonium ions. This diazonium ions combine with DNA to form adducts.

Ketones

Acetone is created by hepatocytes via decarboxylation of extra acetyl-CoA, which derive from glucose metabolism and fatty acids [304]. The concentration of acetone in breath is not only associated with uncontrolled diabetes and glucose metabolism but also with ventilation, cardiac output, physical exercises or ketonemia. Usually, acetone is a good interpreter of ketosis. Acetones including ketone bodies are formed under metabolic conditions related with a high oxidation rate of fatty acids in lung cancer as well as with a weight loss. The liver produces significant amounts of β-hydroxybutyrate and acetoacetate. Acetoacetate goes through spontaneous decarboxylation to yield acetone frequently. Acetone is produced in smaller amounts than other ketone bodies and is exhaled via the breath because of its high vapour pressure. Ketone bodies are also derived from the amino acid metabolism. Under normal conditions, during the day the rate of tissue protein catabolism is more or less constant. However, protein metabolism and, thus, the amount of ketone bodies are increased in cachexia, which is associated with advanced cancer and other diseases. The formation of ketone bodies in general and of acetone, in particular, occurs mostly in the final stages of the disease when cachexia usually occurs [305].

Esters

Esters could be found in large quantities from usual sources such as fatty oils and fats, waxes, and fruit ethers or essential oils. Esters are fragmented into acid and alcohol via hydrolysis.

In humans, specific enzymes, or esterasecan hydrolyzesesters at temperatures below 40°C. One of the enzymes, lipase, which catalyzes the process of lipid hydrolysis.

Nitriles

Acetonitrile is another component of tobacco smoke that was found in both breath and cell culture samples [306]. Bajtarevic, et al. reported that as compared to lung cancer ex-smokers, lung cancer smokers have a higher concentration of acetonitrile in the breath. Though in comparison to healthy smokers, Kischkel, et al. found acetonitrile in higher concentration in lung cancer ex-smokers. Similar results were published for a higher concentration of acetonitrile in smokers in comparison to non-smokers which is consistent with previous observations in urine and blood specimen. The proposed pathway is the biotransformation of acetonitrile by cytochrome p450 monooxygenase to cyanohydrine, which further decomposes spontaneously into formaldehyde and hydrogen cyanide. The acetonitrile metabolism in the body is quite slow. Therefore, substantial amounts of acetonitrile are excreted via exhaled breath and urine.

Aromatic compounds

Aromatic compounds e.g. styrene, toluene, 2, 5-dimethylfuran, benzene, are considered exogenous pollutants [307]. Exogenous origin consists of exposure to cigarette smoke, alcohol, pollution, and radiation. Since these molecules are highly reactive, they escape into the cytoplasm, attacking organs or organelles in the body and causing peroxidative damage to proteins, PUFA, and DNA. This damage accumulates during life and is assumed to lead to age-dependent diseases such as cancer. It is reasonable to assume that cancer patients that have been exposed to excessive smoking and/or have experienced continuous occupational exposure to such exogenous compounds might uptake the compounds in the fatty tissues of the body. These absorbed compounds might be then released slowly and constantly into the breath. In the enzymatic defence reaction, the compound is first functionalized by phase-I enzymes, usually by the cytochrome p450 enzyme system, and then conjugated to other soluble and excretable form by some other enzyme systems e.g. sulfotransferases, glutathione S-transferases, and N-acetyltransferases [308].

STORAGE CONTAINERS

There are various kinds of containers where gaseous samples may be collected however the stainless steel canisters are frequently used because of their properties [309]. Being durable and long lasting, stainless steel canisters are complicated to make and expensive to purchase. In comparison, Polymer bags are more accepted simply because they are really simple to use, cheap, inert and relatively durable. A variety of bags can be cleaned and reused, whereas some are disposable, e.g. Nalophan® (polyethylene terephthalate). Damage from reuse can influence the inertness of the bag and likewise lead to increased substance adsorption into the inner wall.Different bags have different storage properties. Tedlar® bag (E.I. du Pont de Nemours and Company, Wilmington, DE, USA) which happens to be the most often used polymer bag and, together with Mylar® bags, is usually recommended regarding the offline study of FENO [310]. Bio-VOC™ Sampler (Markes International, Llantrisant, Wales, UK) (a late expiratory breath sampler), breath collection apparatus (BCA, Menssana Research Inc., Newark, NJ, USA), and glass vials (along with gas-tight syringes) are also utilised for breath collection [311]. It may also be good for multiple VOC trapping devices. Previous study shows BCA and Bio-VOC™ Sampler devices possess the same when considering of collecting late expiratory air. The mechanism of collection and structure of VOCs has potential differences in different collected compounds; e.g. BCA is a lengthy tubular structure where air flows downstream and of course the air near to the mouth is collected whereas Bio-VOC™ Sampler is a limited storage reservoir in which air is continuously displaced as breathing continues. It is acceptable during the storage for the storage of sulphur compounds and acetone for as much as six hours with minimal loss and HCN for six hours with 35% loss [312]. Nalophan and FlexFoil® bags have already been described to point out no significant loss of contents duringthe early six hours [313], unlike Teflon® (polytetrafluoroethylene) which demonstrated losses of between 10% and 20%. All bags showed significant losses at 24 hours. There are some limitations too as the BCA provides a heated component, whilst the Bio-VOC™ Sampler doesn't and obtained VOC profiles may vary. The speed of reduction in volatile concentration is higher when bags are stored at room temperature in comparison with body temperature, possibly on account of sample condensation and adsorption into the bag's inner surface.

CONCLUSION AND FUTURE PERSPECTIVE

This article discusses the idea of breath analysis as a rapid, valuable and non-invasive diagnostic technique and also VOCs as a biomarker of some well-known diseases or metabolic disorders. VOCs supply helpful information on morbid condition, such as infection or metabolic disorder. Even though promising results with single biomarker have been reported for certain diseases, a combination of several biomarkers is also identified for most of the diseases. Furthermore, the similar marker may not be specific for a certain disease but it might be characteristic of several types of

diseases. For example, formaldehyde was suggested to be a potential biomarker for breast, prostate and balder cancers. So, further advance researches must be needed to overcome these problems.

For diagnosis of VOCs as biomarker conventional techniques such as GC, IMS, PTR-MS, SIFT-MS etc along with new developments such as e-nose, laser spectroscopy techniques are also included in this review. These analytical methods for recognition of markers in the breath at ppb or ppt levels may be applied to help the procedure of medical diagnosis. Although some conventional techniques such as SIFT, IMR-MS, and PTR can be successfully used for both quantitative and qualitative analysis, there are some disadvantages too, such as being prolonged, impossibility of real-time measurement, no single VOC recognition, lack of complete profile detection and a limited number of detectable components.

Modern techniques such as e-nose instruments can play an important role in breath study by determination of VOC mixture types and relative molar concentration of VOCs in exhaled breath, which maintain specific breath-print patterns using pattern recognition algorithms. E-nose techniques provide high sensitivity, good precision, short response time, rapid sensor recovery and relatively low identification limits which are desirable characteristics for the recognition and categorization of VOC mixture present in the human breath.

Further, from the survey of metal oxide based VOCs gas sensor, it can be concluded that ZnO, WO_3, In_2O_3, SnO_2 and α- Fe_2O_3 showing nanostructure morphologies such as nanoparticles, nanowires, nanofibers, nanorods and nanotubes are the most promising for analysis of VOCs at few ppb levels. The selectivity remains however an admissible problem of the metal oxide based VOCs gas sensors. Therefore, new metal oxide materials with higher selectivity need to be used for these types of sensors.

Though there are lots of advantages of e-nose instrument, there are some limitations which must be overcome before they may be used in certain medical applications. E-nose sensor often is not sensitive to some substances such as carbon dioxide, and a variety of low molecular weight hydrocarbons which are detectable by the human nose and are influenced by the occurrence of water vapour in breath sample can be inactivated by certain polar compounds. Although individual sensors may be specific to certain classes of VOCs. Another major drawback of e-nose instrument is the lack of standardized methods for the collection of VOC sample, and the particular e-nose device and methods used to create smell-prints.

In spite of collection techniques, breath storage is also a major challenge in breath research studies. The studies on stability of VOCs in different polymer bags show that some polar compounds, including water, disperse somewhat rapidly throughout Tedlar bag walls, while other compounds are quite stable. Apart from the loss of compounds due to diffusion throughout the bag's walls, some compounds can be released by the bags material and gather in the collected air sample. Finally, the concentration of VOCs also depends on breath collection method. Alveolar breath has elevated levels of exhaled compounds than entire breath and also the lowest concentrations of contaminants.

So, VOCs in the breath is an invaluable tool in biomolecular analysis. Each biomarker in specific metabolic disorder (disease) has its own outcome either in dissolved state or in gaseous state. Out of which the gaseous state is more dispersible and escapes more quickly than the dissolved state. Therefore, monitoring such gaseous imprints bring more superiority over dissolved or aqueous state. The process does not involve any chemical conversion to form chromogenic, or traceable units. Thus, it is much moredirect and less time consuming, and few thousand time sensitive over conventional aqueous invasion based methods. Soin conclusion, to fill up the gaps to detect metabolic disorders in real-time at very low concentration invasively, the breath analysis may have the potential to become useful supplementary tool for diagnosis of various diseases in clinical practice. Therefore, further advance research works in VOCs analysis could bridge the gap to afford absolute, accurate, real-time and low cost diagnostic tool that can contribute in diseasescreening among the ever increasing human population. Development of more sophisticated gadgets for sampling and sample analysis of VOCs could be a breakthrough to the biomedical system, and pharmaceutical industry and will be most acceptable and popular diagnostics method in future.

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