Identifying VOC biomarkers of diseases in humans and plants

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Flowers emit odors to attract and stimulate bees and other pollinators. These odors consist of volatile organic compounds (VOCs) which can be detected by bees in low concentrations (ppb to ppt). For bees and other insects, the sense of smell is one of the most important elements for recognizing their environment. Because of their olfactory sensitivity, bees can detect a range of VOCs in different concentrations. VOCs can also act as biomarkers in humans and plants, which means that certain diseases can be identified using these VOCs. Biomarkers are also used for the application of clinical research and drug development. In plants, variations in biotic and abiotic factors result in different VOC emissions. For instance, in plant infestation, the number of insects and temperature variatons, showed different VOC emissions. Furthermore, infected plants emit microbial VOCs caused by bacteria or fungi. Also, plants emit different VOCs depending on their geographical location. In humans, VOCs can mainly be detected in blood, urine, feces and breath. Various VOCs can be detected as a result of an infection. With the help of these VOCs, diseases such as Alzheimer or cancer can be diagnosed in the early stages and can possibly be treated. Since bees can detect certain VOCs in low concentrations, it is possible for bees to detect certain biomarkers. In this way, specialized and complicated methods, which require highly trained personnel and laboratories, are not required for disease detection. This article shows biomarkers of four plant infection diseases, two plant infestation diseases, and 33 human diseases. Besides using bees to detect VOCs, this article also outlines other techniques such as photoionization detection, flame ionization detection, metal oxide detection, and a novel smartphone detection method, which can be used in different settings.

1 Introduction

All participants of the minor Smart Industry, which are students with various backgrounds ranging from automotive to human resource management, have chosen a project from a company to work on during approximately ten weeks to apply their knowledge of Smart Industry. We have chosen to carry out the project of a start-up called InsectSense from Wageningen.

Insectsense is a start-up company that uses insect behaviour for innovative solutions in the diagnostic-device market. They have done a lot of research in the field of olfaction and conditioning of bees. However, the company is still in the early stages and would like to know what options and possibilities there are. Because of this, Insectsense has drawn up various issues that can be addressed in a project for Smart Industry students. One of these issues is to find out what diseases can be indicated by volatile compounds and odors, which will be answered in this report. With the outcomes of the report, Insectsense can proceed faster and more specifically with the formation of a fully-fledged business with which they can enter the market.

To answer the main question, we have drawn up a number of relevant sub-questions, which will form the structure of the report. Their conclusions will contribute to the answer of the main question.

2 Method

The course of actions performed in this research is described as follows. First, we did an extensive study in the field of olfaction of bees. A lot of information was passed to us by our client, who is an expert in the field. Based on this information, we created an understanding of what olfaction is and how bees can detect odors. Next, we studied what odors are and what they consist of. We knew that bees can detect odors, but not specifically the mechanisms behind it. All research described in this report was done by gathering literature. At last, we studied how diseases can be detected by their volatile compounds. We looked at different methods of volatile compound detection and more specifically, how specific diseases can be identified by their volatile compounds.

3 Odors

Flowers attract bees and other pollinators by their odor. It exists of various volatile organic compounds (VOCs), which act to stimulate and guide the pollinators (Knudsen et al., 1993). The volatility of a compound is the degree to which the species tends to transfer from the liquid (or solid) state to the vapor state. At a given temperature and pressure, a highly volatile substance is much more likely to be found as vapor than is a substance with low volatility, which is more likely to be found in a condensed phase (liquid or solid) (Felder & Rousseau, 2005). In the latest EU directive on VOCs, requirements are made for compounds. Namely, a VOC is defined as an organic compound which has an initial boiling point less than or equal to 250 °C measured at a standard pressure of 101,3 kPa (European Parliament and Council, 2004). Predicting if a certain compound based on its molecular structure is a VOC is not straightforward. Vapor pressure data for volatile organic compounds (VOCs) are used for technical purposes in the chemical industry. The demand for accurate data on vapor pressures is not that imperative. The reason is that the uncertainty of risk assessment is predominantly determined by very uncertain toxicological data. For some compounds, however, data found in the literature are deviating unacceptably much even compared with toxicological data. For other compounds, no data on vapor pressure can be found. This is often the case for high boiling compounds (Olsen & Nielsen, 2001).

The perception of an odor is the result of a complex series of events. It involves the interaction of chemicals with olfactory neurons. Neurons express proteins that play a role in transforming this chemical signal into electrophysiological messages that are processed in the brain as an odor (de March et al., 2015). In insects, the sense of smell is one of the most important elements for recognizing the environment. For example, the insects can easily track down plants and flowers through volatile substances that are emitted (Conchou et al., 2019). Furthermore, natural odors are used by animals for mate recognition, food identification, and other purposes (Wright, 2004). Each insect species expresses some olfactory receptors that bind some of the volatile compounds in its habitat (Conchou et al., 2019). In a study from 1992, researchers compiled a list of more than 700 compounds from 441 taxa reported in 118 studies. They found that VOCs in flowers are mainly distributed within three groups: fatty acid derivatives, benzenoids, and isoprenoids. The compounds found in the greatest number of taxa are benzenoids and isoprenoids (Knudsen et al., 1993).

Odors must be detected at concentrations that vary across several orders of magnitude (Wright, 2004). Field trials conducted by Bromenshenk et al. indicated that honeybees are capable of detecting vapor compounds at concentration levels of ppb to ppt. For example, the bees were able to positively indicate the presence of 2,4-DNT generated in an estimated vapor concentration of 50–80 ppt (MacDonald et al., n.d.). However, the stability of the representation of an odor relative to other odors across concentration has not been extensively evaluated. A study showed that pure odorant compounds became progressively easier for honeybees to discriminate with increasing concentration (Wright, 2004). Furthermore, it depends on which honeybees are used in detecting volatile compounds. There are two types of honeybees relevant when detecting odors. Hygienic and non-hygienic bees. Hygienic bees are able to detect, uncap, and remove diseased brood, which is a fungal disease, from the nest before the pathogen sporulates and becomes infectious (Woodrow & Holst, 1942). In a study, researchers concluded that three-week-old hygienic bees were able to discriminate between the brood odors significantly better than three-week-old non-hygienic bees at lower concentrations (R. et al., 2001). Therefore, hygienic bees are most likely more sensitive to detect odors.

4 Detecting VOCs

Bees can accurately detect VOCs because of their olfactory sensitivity. However, it is not the only method to detect VOCs. This section outlines a few methods which are used in different settings for different purposes.

A photoionization detector (PID) can analyze a wide spectrum of chemicals, including aromatic hydrocarbons, but excluding low molecular weight hydrocarbons. PID uses ultraviolet light to break down airborne VOCs into either positive or negative ions. Once the VOCs are broken down, the detector can measure or detect the charge of the ionized gas. Keep in mind that PID only changes the VOC sample for a short time. It detects it but does not permanently change them. Methylene chloride is an example of a dangerous VOC PID is useful in detecting (Lafond, 2018).

Flame ionization detection (FID) is a technique that is often used in the automotive industry and is used as the standard in measuring hydrocarbons emission. It works by putting a sample gas into a hydrogen flame which makes any hydrocarbons within the gas sample start to produce ions. These ions are the being detected with a metal detector (Lafond, 2018).

Metal oxide semiconductor sensors (MOS) can detect a wide variety of gases, for example: benzene, ethanol, and toluene. They use a sensitive film that reacts with gases and can produce a signal when they reach toxic levels. Because MOS sensors can work in low humidity, they are really effective (Lafond, 2018).

In a recent study, a smartphone-based sensing system was developed for monitoring VOCs in real-time using alternative current (AC) impedance measurement. The interdigital electrodes modified with zinc oxide (ZnO), graphene, and nitrocellulose were used as sensors to produce a response to the VOCs. The smartphone-based system was demonstrated to detect acetone at concentrations as low as 1.56 ppm, while AC impedance spectroscopy was used to distinguish acetone from other VOCs. Finally, measurements of the exhalations from human being were carried out to obtain the concentration of acetone in exhaled breath before and after exercise. The results proved that the smartphone-based system could be applied on the detection of VOCs in real settings for healthcare diagnosis. Thus, the smartphone-based system for VOCs detection provided a convenient, portable and efficient approach to monitor VOCs in exhaled breath and possibly allowed for early diagnosis of some diseases (Liu et al., 2017).

5 Biomarkers

The term 'biomarker' is a very broad term as it indicates a marker that can be objectively measured that reflects a biological process. Relevant biomarkers are used to measure either for the purpose of drug development or for application at the patient level in the clinic. Biomarkers are noted with a wide range of technologies. These technologies are used to measure the variety of biomarkers, from fluid biomarkers, cellular biomarkers, tissue-based biomarkers, imaging biomarkers and other physiological measures (Amaravadi, 2016). In a recent COVID-19 study, researchers found that patients who are diagnosed with COVID-19 and have cardiac biomarker elevations are significantly more associated with 28-day death than in patients who don't have these cardiac biomarker elevations (Qin et al., 2020). Thus, it shows that biomarkers can give subtle, but essential information.

5.1 Plant diseases

Besides attracting pollinators, plants emit VOCs to protect themselves from insects and pathogenic attack (Baldwin, 2010). Therefore, these volatiles can be seen as biomarkers in plants. Some VOCs are emitted from a wide range of plants while other VOCs are emitted from specific plant taxa. Thus, volatile emissions typically differ between plant species. Also, many biotic and abiotic factors have influence on these emissions (Conchou et al., 2019); A specific plant from one climate has other emissions than the same plant in another climate. This makes it difficult to successfully point to certain VOCs as biomarkers for specific diseases.

Diseases can be caused by virusses, bacteria or fungi which can be classified as infections. Besides this, diseases can also be caused by insects which is called infestation. In this section the effect on emitted VOCs because of these two types of diseases will be explored.

5.1.1 Infections

Bacterial taxa including plant pathogens can be identified with the help of ribosomal gene sequencing (Han, 2006). While this method yields the most accurate results, it is also expensive, time-consuming, and requires specialized personnel (Tothill, 2001). Researchers showed that microbial species such as bacteria and yeasts can be identified using VOC detection (Gibson et al., 1997). More than 1000 different microbial VOCs (mVOCs) have been reported in the literature (Lemfack et al., 2018). Also, VOC detection can be applied to detect off-odors which is a sign of past or present microbial activities (Jonsson et al., 1997). It is unrealistic to cover all diseases in different plants. Therefore, a small selection is made to show that disease identification with the help of VOC is viable. A summary can be found in table 1.

The pathogen *Erwinia amylovora* is the causal agent of fire blight in pomaceous plants. This is the most serious bacterial disease of apple and pear trees. Fire blight is able to destroy an entire tree in a single growing season. In the early stages of the disease, there are no obvious symptoms and in later stages, it is difficult to control the pathogen. In a study, researchers concluded that there are subtle differences in which VOCs are emitted from each different strain of *E. amylovora*. However, the most abundant VOCs are 3-methyl-1-butanol, 3-hydroxy-2-butanone, and phenylethyl alcohol (Spinelli et al., 2012).

Botrytis cinerea has a very wide host range and is known as a fungal pathogen that causes gray mold. In different hosts, *B. cinerea* utilizes different infection mechanisms. Conidial germ tubes can penetrate wounds or natural openings, but it can also directly penetrate and destroy healthy plant tissue (Jarvis, 1977). Symptoms are also different from host to host. In grapes, it results in softening and rot (McClellan &

Disease	Pathogen	Host	Biomarkers	Location	References
Fire blight	*Erwinia Amylovora*	Apple	3-methyl-1-butanol, 3-hydroxy-2-butanone, and phenylethyl alcohol	New Zealand	Spinelli et al. (2012)
Gray mold	*Botrytis Cinerea*	Tomato	α-Copaene	The Netherlands	Thelen et al. (2005)
Powdery mildew	*Oidium neolycopersici*	Tomato	1,6-anhydro-β-D-glucopyranose, (Z)-3-heptenol, and 1-fluorododecane	United Kingdom	Laothawornkitkul et al. (2008)
Basal rot	*Fusarium oxysporum* and *Fusarium proliferatum*	Onion	1-propanol, 2-methyl-1-propanol, and ethanol	Finland	A. Wang et al. (2018)

Table 1: *Summary of emitted VOCs of diseased plants*

Hewitt, 1973). Not in all hosts, it ends catastrophically. In tomatoes, *botrytis* spots or ghost spots occur after penetration of *B. cinerea* germ tubes, which leads to a halo on the tomato, and this results in a non-exportable product and lower price, but doesn't affect its quality or taste (Verhoeff, 1970). After VOC identification, researchers concluded that α-copaene is the most noticeable VOC induced by the tomato leaf-*Botrytis cinerea* interaction (Thelen et al., 2005). Another disease in tomato plants is powdery mildew which is caused by a biotrophic pathogen known as *Oidium neolycopersici*. Researchers identified multiple VOCs that weren't emitted when the tomato plant was infected by the necrotrophic *B. cinerea*. Therefore, these volatiles are good candidates as specific biomarkers for powdery mildew in tomato plants. These compounds are: 1,6-anhydro-β-D-glucopyranose, (Z)-3-heptenol, and 1-fluorodode-3-heptenolcane (Laothawornkitkul et al., 2008).

Another common disease is basal rot which appears in onions and is mainly caused by the fungi *Fusarium oxysporum* and *Fusarium proliferatum*. This disease is recognized as one of the most serious onion diseases and causes major problems (Haapalainen et al., 2016). In a recent study, researchers concluded after conducting experiments, that in total 42 VOCs were emitted from basal rot onions. Among those compounds, the concentration of 31 compounds were higher in *Fusarium* samples, whereas the concentration of 11 compounds were higher in the control onions. The most abundant compounds emitted from the *Fusarium* samples were 1-propanol, 2-methyl-1-propanol, and ethanol (A. Wang et al., 2018).

5.1.2 Infestation

Greening is one of the most serious citrus diseases and the insect *Diaphorina citri* is the main vector of the disease (Jagoueix et al., 1994). In a study that focussed on *Diaphorina citri* infested Valencia sweet orange plants, researchers found that compared to the healthy plants, there was a decrease in sesquiterpenes and green leaf volatiles in the infested plants. However, there was an increase in monoterpenes. The volatile profile was similar to the control leaves except for two VOCs that were increased (linalool and *d*-limonene) and were five compounds decreased ((*E*)-2-hexen-1-ol, (*E*)-2-hexanal, 2,4-nonadienal, citronellal, and δ-3-carene. In total, 21 VOCs were affected by infestation. Seventeen compounds were significantly higher than the control leaves. From these compounds, fourteen were monoterpenes, and three were sesquiterpenes (Hijaz et al., 2013). See table 2 for the specific VOCs.

In another study, researchers did experiments with different insect population sizes and temperature changes, and the effects on VOC emission of plants. They took 0, 30, 70 and 100 adult *Myzus persicae* per plant (*Arabidopsis thaliana*). They noticed that the proportion of terpene significantly increased as the population size grew and was at the population size of 100 the highest. The total alcohol percentage significantly decreased as population size grew. Also, significant changes in total aldehyde proportion were seen between infested and control plants, but irrespective of population size. The compound 4-methylpenthyl isothiocyanate significantly increased with the number of insects feeding on the leaves, whereas this compound has not been detected in uninfested plants (Truong et al., 2014). This shows that choosing VOC biomarkers for potentially infested plants, is highly dependent on

Insect	Host	Biomarkers	Location	References
Diaphorina citri	*Citris sinensis*	α-pinene, sabinene, pinene, myrcene, ocimene, *t*-sabinene H2O, γ-terpinene, linalool, (*Z*)-citral, δ-3-carene, α-phelandrene, α-terpinolene, neral, and β-fenchyl alcohol, β-elemene, α-humlene, and (*E*)-β-caryophllene	Spain	Hijaz et al. (2013)
Myzus persicae	*Arabidopsis thaliana*	2-ethyl-hexan-1-ol, 6-methyl hept-5-en-2-one, (*Z*)-3-hexenyl acetate, phenylacetaldehyde, 4-methylpentyl isothiocyanate, (*E*,*E*)-α-farnesene, 5-(methylthio) pentanenitrile, and dimethyl trisulfide	Texas, USA	Truong et al. (2014)

Table 2: *Summary of emitted VOCs of infested plants*

the population size of the specific plant.

In total twenty compounds were detected with a range of 17 °C to 32 °C. A significant decrease was seen in alcohol proportions. Consididering individual compounds, 2-ethyl-hexan-1-ol decreased significantly, whereas 4-methyl-1-penten-3-ol increased. (*Z*)-3-hexen-1-ol and decan-3-ol were only detected in infested plants at the highest temperatures. Most of the emission of esters, aldehydes and 6-methyl-hept-5-en-2-one, ketone were affected by high temperature in combination with infestation. The individual ester compounds 1-methylcyclopentyl acetate, methyl 2-ethylpentanoate, and (*Z*)-3-hexanyl acetate showed a significant increase in infested plants at high temperatures Truong et al., 2014. This shows that temperature is important considering the VOC emissions of infested plants. Therefore, it is not straight-forward to point to specific biomarkers as a sign of infestation. In table 2 compounds are listed that increased the most.

5.2 Human diseases

A study of devices that analyze human respiration indicates that volatile metabolites, known as biomarkers, can detect specific diseases in humans (Wilson, 2018). Think of metabolic disorders, various cancers, chronic lung diseases, etc., but also the general health of patients (Buljubasic & Buchbauer, 2015). Biomarkers are mainly of two categories, organic compounds, and volatile metabolites (Wilson, 2018). Most diseases can be detected with VOCs. These VOCs can mainly be detected in urine, feces, blood, and breath of humans (Probert et al., 2009). A list of different diseases and their biomarkers is shown in table 3 which can be found in appendix A.

Air exhaled by humans contains thousands of volatile organic compounds. The composition of these substances varies and is largely dependent on the health of the person concerned. Metabolic processes create volatile substances that end up in the blood. These are then passed on to someone's breath as soon as the blood reaches the lungs. Certain unique VOC patterns are generated during chronic inflammation and oxidative stress. Measuring VOCs in breath can thus become an important factor for clinical diagnosis. A common biomarker of exhaled air is nitric oxide, where elevated values occur in pneumonia and oxidative stress gives increased values when someone has a chronic lung disease, for example, asthma and obstructive lung disease (Boots et al., 2012).

A correlation between a pattern and the concentration of VOC can prevent various diseases. This results in a better diagnosis and monitoring of pathological processes and the assessment of pharmacological response. This way can be simple, acceptable, and fast for patients to detect diseases. Volatile organic compounds can be odorous and can be emitted through respiration to assess gastrointestinal and liver diseases.

Research has shown that specific changes occur in the VOCs when someone has intestinal, stomach, or liver problems. These changes can be used for clinical diagnosis (Probert et al., 2009).

Body odors that are emitted as volatile substances can be used to detect various diseases. For example, diseases such as cancer, infections, metabolic disorders, and other diseases can change components in the VOCs, which can be traced back to biomarkers of diseases. This can lead to a new era of disease diagnosis. The sudden change of smell in urine or breath can be due to one of the above diseases. Every day the human body emits odors (VOCs) with different parts, each of which has a different odor. Genetic disorders, pathological diseases, or psychological conditions result in changing VOCs and therefore also in odor. This can make it an important part of early disease detection. The image below shows the most common VOCs that occur in lung cancer (Buljubasic & Buchbauer, 2015).

Various fingerprints are presented of diseases that can be detected by changes in VOCs. Most VOCs are released through breathing. For example, lung cancer can be detected quickly and can be tackled at an early stage. Various diseases such as bladder, ovarian, and prostate cancer can be diagnosed using VOCs in the urine. Metabolic and genetic disorders, also known as metabolic diseases, can often be detected in the early years due to an unusual odor. Patients with kidney failure are known to have an ammonia-like odor in urine, and in diabetes, urine has an acetone-like odor. Research has shown that animals can play a role in smelling and detecting disease. Trained dogs can accurately distinguish between patients who have cancer and healthy patients utilizing breath and urine samples (Buljubasic & Buchbauer, 2015). In this way, diseases can be detected much earlier, so that action can be taken more quickly. Besides that, it's also a friendly way for patients to detect possible diseases (Wilson, 2018).

Research has shown that diseases, due to vector pathogens (malaria), determine a certain odor. It is suggested that Malaria generates volatiles that can be detected by smell. For example, it has been proven that vector mosquitoes can distinguish between an infected and uninfected person from malaria using smell. This has created many opportunities for volatile diagnostics for malaria (Stanczyk et al., 2018).

Often, Alzheimer's disease is not diagnosed until a late stage in the disease process. It is often at that moment that it is too late to intervene and the patient can no longer be cured. This makes it extremely important that the disease is discovered several decades before the onset of the typical symptoms to prevent worse. One method used to determine this is to analyze exhaled VOCs. These VOCs can provide a picture of a patient's physiological state and correlate with neuro-generative diseases such as Alzheimer's (Emam et al., 2020).

6 Conclusion

This article investigated the following research question: "what diseases can be indicated by volatile and odor (human and plant)?" Odor can be detected by various volatile organic compounds (VOCs) that a human or plant emit. In insects, the sense of smell is one of the most important elements for recognizing the environment. For example, insects can smell plants and flowers from great distances utilizing the receptors and recognize them using the released VOCs. Bees can even detect vapor compounds in parts per billion and parts per trillion. These insects are therefore extremely suitable for detecting various VOCs. Almost all biological processes, such as diseases, have certain biomarkers that reflect the process and are often measurable. Relevant biomarkers are used for the application of clinical research and drug development. These biomarkers can be found in VOCs and contain essential information for diagnoses of plant and human diseases. For example, it has been proven that microbial species such as bacteria and fungi in plants can be identified through VOC detection by bees. In this way, diseases and bacteria can be detected in time, so that they can be tackled. It has also been shown that diseases in humans can be detected by biomarkers from volatile metabolites. Think of different types of cancer, metabolic disorders, chronic lung diseases, etc. These VOC biomarkers can be detected in urine, feces, blood, and veins of humans. Most VOCs are released through breathing. A relationship between a pattern and the concentration of VOCs can prevent various diseases. This results in better diagnosis and monitoring of pathological processes and the assessment of pharmacological response. This way can be simple, acceptable, and fast for patients to detect diseases and to intervene early. VOCs often give off a certain odor in diseases. Due to their excellent sense of smell, bees are a suitable means of detecting these VOCs in diseases. Diseases in plants and humans contain a certain odor that can be detected by VOCs. This makes it possible to detect these diseases by odor and volatility and bees are suitable for detecting this because of their strong sense of smell. This article has not investigated the minimum concentration, accuracy, and reliability per disease to detect it. There was simply too little information available about this and the authors of this paper have limited biological knowledge. This could be examined per disease in a follow-up study.

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A Biomarkers of human diseases

Disease	Clinical sample	Biomarker	Reference
ALS	blood	butylated hydroxy-toluene	Jiang et al. (2015)
Bovine TB	breath	2,2-dimethyl undecane	Peled et al. (2012)
Cholera	feces	p-menth-1-en-8-ol	Probert (2004)
Cryptosporidiosis	feces	indole	Chappell et al. (2016)
Endometriosis	endometrial tissue	hypoxanthine	Li et al. (2018)
HNC	urine	2,6-dimethyl-7-octen-2-ol	Taware et al. (2017)
RCC	urine	2,5,8-trimethyl-1,2,3,4-tetrahydonaphthalene-1-ol	Monteiro et al. (2017)
Stomach ulcer	breath	2-butanone	Ulanowska et al. (2011)
Breast cancer	breath	2-propanol, 2,3-dihydro-1-phenyl-4(1H)-quinazolinone, 1-phenyl-ethanone, heptanal, and isopropyl myristate	Phillips et al. (2006)
Asthma	breath	NO, pentane, ethane, nitric oxide, prostaglandin E2, leukotriene B4, and 8-isoprostane	Olopade et al. (1997), Paredi et al. (2000), Montuschi et al. (1999), A. D. Smith et al. (2004), Kostikas et al. (2003), Kostikas et al. (2005)
COPD	breath	NO, 8-isoprostane, leukotriene B4, and H2O2	Corradi et al. (1999), Corradi et al. (2003), van Beurden et al. (2002), Borrill et al. (2007), Kostikas et al. (2005)
Hepatic coma	breath	Methyl-mercaptan, and dimethyle sulphide	Hisamura (1979), Hiroshi et al. (1978)
Diabetes mellitus	breath	Acetone, ethanol, and methyl nitrate	Novak et al. (2007), Galassetti et al. (2005), P. Wang et al. (1997)
Schizophrenia	breath, sweat	Carbon disulphide, trans-3-methyl-2-hexenoic, and pentane	Phillips et al. (1993), K. Smith and Sines (1960), K. Smith et al. (1969)
Oxidative stress	breath	Ethane, pentane, and hydrocarbons	Amann (2005)

Lung cancer	blood, breath	Styrene, 2,2,4,6,6-pentamethylheptane, 2-methylheptane, decane, ethylbenzene, trimethylbenzene, benzene. octane, pentamethylheptane, cyclopentane, 3-methyl-1-hexene, 3-methyl-1-heptene, 1,4-dimethylbenzene, 2,4-dimethylheptane, hexanal, isoprene, 2-methylpentane, xylenes, heptanal, cyclohexane, butylated hydroxytolune, 1-butanol, 3-hydroxy-2-butanone, o-toluidine, protonated formaldehyde and a fragment of protonated iso-propanol	Amann (2005), Wehinger et al. (2007), Phillips et al. (1999), Deng et al. (2004), Yu et al. (2005), Poli et al. (2005), Bajtarevic et al. (2009), Song et al. (2010), Skeldon et al. (2006), Hakim et al. (2012), Preti et al. (1988), Crohns et al. (2009)
Cholesterol metabolism	blood	Isopropene	Amann (2005)
Ketonemia	blood	Acetone	Amann (2005)
Liver impairment	blood	Sulfur-containing compounds (dimethylsulfide, methyl mecraptane, ethyl mercaptyne)	Amann (2005)
Uremia, kidney impairment	blood, urine	Nitrogen-containing compounds (ammonia, dimethylamine, trimethylamine)	Amann (2005)
ALFD	breath	Acetaldehyde, and isoprene	Netzer et al. (2009)
ARDS	breath	Acetone, isoprene, and n-pentane	Scholpp et al. (2002), Schubert et al. (1998)
Cystic fibrosis	breath	pentane, dimethylsulfide, carbonyl sulfide, carbon disulfide, nitrotyrosine, leukotriene B4, interleukin-6, and 2-propanol	Barker et al. (2006), Kamboures et al. (2005), McGrath et al. (2000), Balint et al. (2001), Carpagnano et al. (2003)
Ketosis	breath	acetone	Likhodii et al. (2002)
IBD	breath	Ethane, propane, and pentane	Pelli et al. (1999), Sedghi et al. (1994), Ondrula et al. (1993), Kokoszka et al. (1993)
ILD	breath	Ethane	Kanoh et al. (2005)
Hyperglycemia	breath	Acetone, ethanol, methyl nitrate, and ethylbenzene	Lee et al. (2009)
Liver cirrhosis	breath	Methyl mercaptan, and dimethyl sulfide	Kaji et al. (1978)
Chronic hepatitis	breath	dimethyl sulfide	Kaji et al. (1978)
Rheumatoid arthritis	breath	pentane	Humad et al. (1988)
COVID-19	breath	Ethyl butanoate, butyraldehyde, and isopropanol	Chen et al. (2020), Shan et al. (2020)

Malaria	blood, breath	Gametocytes, 3-methyl butanoic acid, 2-methyl butanoic acid, hexanoic acid, tridecane-4-hydroxy-3-methylbut-2-enylpyrofosfaat, α-pinene, 3-carene, nonanal, hexanal, plasmodium, and tridecane	Moraes et al. (2014), Stanczyk et al. (2018), Berna et al. (2018)
Alzheimer	breath	apolipoprotein E4 allele, hexanal, 5-methyl-undecane, butylated hydroxytoluene, pivalic acid (2,2-dimethylpropanoic acid), and 2,3-dimethylheptane	Mazzatenta et al. (2015), Emam et al. (2020)

Table 3: *List of diseases and their biomarkers*