Review Article

Narrative review on artificially intelligent olfaction in halitosis

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Abstract

Halitosis, commonly known as oral malodor, is a multifactorial health concern that significantly impacts the psychological and social well-being of individuals. It is the third most frequent reason for individuals to seek dental treatment, after dental caries and periodontal diseases. For an in-depth exploration of the topic of halitosis, an extensive literature review was conducted. The review focused on articles published in peer-reviewed journals and only those written in the English language were considered. The search for relevant literature began by employing subject headings such as 'halitosis, oral malodor, volatile sulfur compounds, artificial intelligence, and olfaction' in databases such as PubMed/Medline, Scopus, Google Scholar, Web of Science, and EMBASE. Additionally, a thorough hand search of references was conducted to ensure the comprehensiveness of the review. After amalgamating the search outcomes, a comprehensive analysis revealed the existence of precisely 134 full-text articles that bore relevance to the study. Abstracts and editorial letters were excluded from this study, and almost 50% of the full-text articles were deemed immaterial to dental practice. Out of the remaining articles, precisely 54 full-text articles were employed in this review. As primary healthcare providers, dentists are responsible for diagnosing and treating oral issues that may contribute to the development of halitosis. To effectively manage this condition, dentists must educate their patients about the underlying causes of halitosis, as well as proper oral hygiene practices such as tongue cleaning, flossing, and selecting appropriate mouthwash and toothpaste. This narrative review summarises all possible AI olfaction in halitosis.

Keywords: Artificial Intelligence, halitosis, odorify, olfaction, oral croma

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INTRODUCTION

The field of dentistry is increasingly turning to artificial intelligence (AI) to revolutionise patient care and increase productivity.[1] AI technology was first proposed by Alan Turing, who believed human competency depended on knowledge and logical reasoning.[2] Newell and Simon's creation of 'The Logic Theorist' in 1955 marked a significant milestone in AI's development and implementation in various fields, including dentistry.[3,4] Halitosis, a condition resulting in an unpleasant odour in exhaled air, is classified by the American Dental Association into genuine halitosis, pseudo-halitosis, and

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halitophobia.[5,6] With up to 50% of adults affected by halitosis, AI has the potential to aid in the diagnosis, treatment, and management of halitophobia. Dentists must remain informed about potential AI applications and benefits as the field continues to advance.[7,8]

The olfactory sense is responsible for detecting and distinguishing various environmental compounds in the air.[9] Anosmia, which has become more prevalent during the COVID-19 pandemic, can significantly decrease one's quality of life by reducing olfactory stimulation.[10,11] Odorant receptors in the nasal cavity are responsible for the sense of smell by detecting odorants and transmitting neural signals to the brain for processing. Humans have roughly 400 different types of olfactory receptors, which are capable of detecting millions, if not billions, of distinct odorant molecules.[12]

Halitosis, commonly known as bad breath, is caused due to various factors such as the presence of bacteria, cratered tongue surface, xerostomia, the presence of dental caries, which are extensive, systemic diseases such as diabetes, liver and kidney disease, smoking, fixed dentures etc., all can contribute towards this condition. Oral halitosis contributes to the formation of volatile sulphur compounds (VSCs) produced by bacteria in the mouth. VSCs are highly volatile and have a low odour threshold, making them the most common indicator of halitosis.[13] However, relying solely on VSC detection for diagnosis has its limitations, as some non-sulphur volatile chemicals and other disorders can also lead to halitosis in the absence of VSCs. The conventional or the traditional approach towards detecting halitosis remains to be the organoleptic approach, wherein the degree of unpleasantness in the exhaled air from the mouth and nose is evaluated. To address these limitations, an artificial olfaction approach has been developed using analytical software and a database of breath patterns to evaluate a wide range of oral volatile chemicals noninvasively.[14] Nanomaterial-based sensors are capable of assessing the composition of oral breath, and a decision tree classifier is used to identify the presence of extra-oral or oral halitosis, as well as to examine the connection with systemic disorders if the halitosis is not oral in origin. In 2017, 20 functionalised nanomaterial-based sensors were developed, which were able to analyse exhaled air with high accuracy (86%) and distinguish between 17 different systemic disorders.[15] Moreover, preclinical, experimental evaluations have shown that the sensitivity of these sensors can be improved through the use of target volatile organic compounds (VOCs)/VSCs artificial gas combinations for training.[16]

Halitosis detection has been a topic of interest for a significant period, with organoleptic scoring being the primary method. However, recent advancements in artificial olfaction have revolutionised halitosis detection, making it more efficient. Nanomaterial-based sensors are now employed to differentiate between volatile and non-volatile compounds and intra and extra-oral halitosis. Machine learning techniques have also been incorporated in halitosis detection to detect smells, which serve as reference objectives and for independent recognition. In this review article, we discuss the different analytical approaches in use and the potential value of artificially intelligent olfaction in halitosis detection. This narrative review also provides insights into newer approaches and how they differ from traditional methods, as well as the treatment of halitosis.

MATERIALS AND METHODS

The following keywords were used to conduct a thorough literature search in the PubMed, Web of Science, EMBASE, Scopus, and Google Scholar databases: ([artificial intelligence OR artificial olfaction]) AND [Olfaction OR artificial smell OR E-Nose]), ([halitosis OR exhaled breath OR exhaled compounds OR exhaled breath analyser]) AND [VOCs OR volatile compounds OR VSCs]) let this be maintained. A total of 134 studies were purged, including duplicates and non-English research [Figure 1]. Studies that were not pertinent to the subject were removed from the remaining titles and abstracts, along with articles whose full texts could not be retrieved. The remaining papers' titles and abstracts were scrutinised, and research irrelevant to the topic and publications for which there was no full text available were also disregarded. The results of the 22 studies that met our inclusion criteria are summarised in this review. Most of them concentrated on VOC structure, composition, and detection, emphasising the chemicals' significance as biomarkers in halitosis detection.

VOLATILE COMPOUNDS STRUCTURE AND COMPOSITION

Structure and Composition of VOC

Volatile organic compounds (VOCs) are low-molecular-weight carbon-containing substances that possess high vapour pressure and hydrophobicity, which are commonly referred to as odorant molecules.[17] These molecules arise primarily from chemicals that volatilise at room temperature and enter the nose, but their odour intensity cannot be determined by vapour pressure measurement. Organic and inorganic compounds can both cause odour, indicating that odorant molecules are not solely carbon-containing substances.

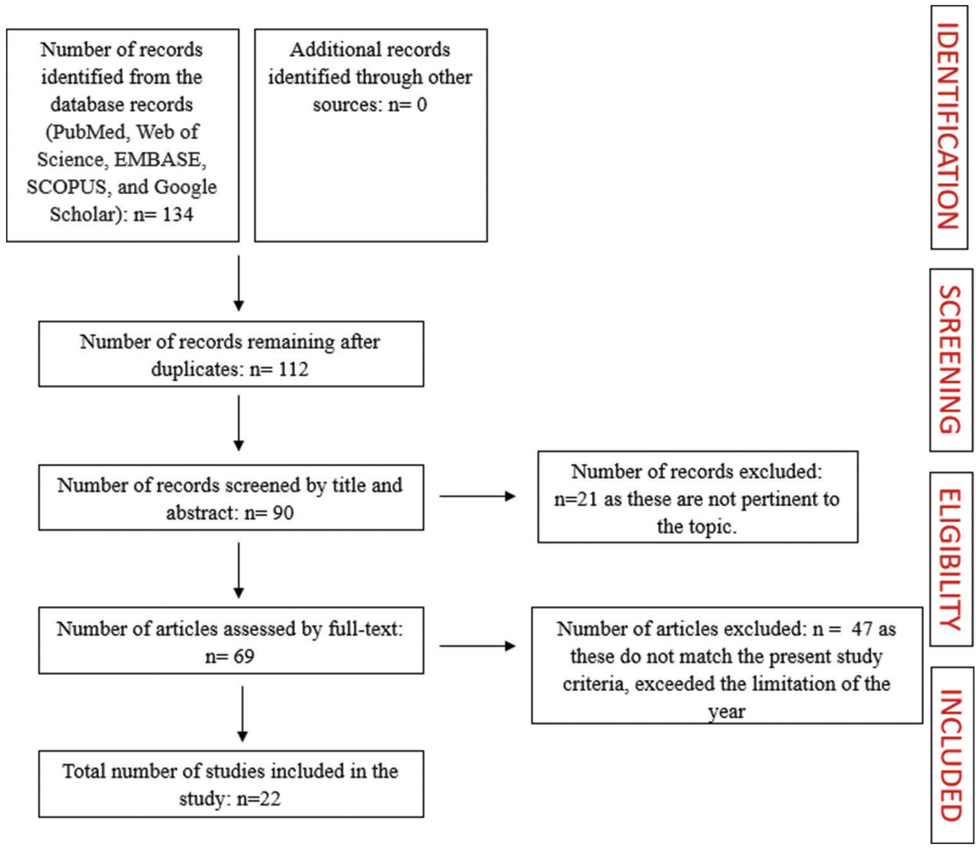

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Ammonia (NH3), for example, emits a fishy scent, while elemental chlorine gas (Cl2) has an unpleasant odour. Hydrogen sulfide (H2S) has a foul rotten egg odour.[18,19]

Functional groups are more easily and quickly identified by humans than single elemental components, such as thiols (-SH), oxides (-NOH), and nitro groups (-NO2), which each have a distinct sulphurous, camphoraceous, or sweet-ethereal aroma.[19] A molecule's functional group is the only predictor of its odour since other compounds may have the same functional group but different scents. For example, 4,4-dimethyl-2-octene-lactone, 8, methyl-2-noneno-lactone, and 5,6,6-trimethyl-2-hepteno-lactone all have distinct minty, buttery, and terpene-like scents, respectively. Even though enantiomeric molecules, also known as optical isomers, have the same chemical properties, only 5% of enantiomer pairings have a comparable fragrance. For instance, both the lemon and orange aromas of limonene's two enantiomers may be found in (R)-(+)-limonene.

CLINICAL ASSOCIATION OF VSCS WITH HALITOSIS

Halitosis, a condition marked by high levels of VSCs, can be caused by gram-negative microbes like *Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia*.[20-22] These microbes are associated with periodontal disorders, and deeper periodontal pockets can lead to higher VSC levels.[23] VSCs are primarily composed of hydrogen sulfide (H2S), methyl mercaptan (CH3SH), and dimethyl sulfide (CH3SCH3), with hydrogen sulfide being the most commonly observed VSC in periodontal pockets.[24-26] Multivariate data analysis techniques like principal component analysis (PCA) can be used to examine breath measurement data and visually depict multidimensional data in a plane.[27,28]

USE OF AI IN HALITOSIS DETECTION

EBA

The exhaled breath of humans is primarily composed of nitrogen, oxygen, hydrogen, carbon dioxide, inert gases, and water vapour, as well as organic and inorganic VOCs.[29-31] These VOCs encompass a variety of chemical compounds, including acetone, ethanol, ethane, isoprene, methane, pentane, carbon monoxide, nitric oxide, nitrous oxide, ammonia, and hydrogen sulfide. While certain VOCs are produced by both normal and abnormal cells, others are only present in abnormal cells, making the VOC pattern a valuable tool for diagnosing and treating various conditions.[32] Exhaled breath analysis (EBA) is an inexpensive, noninvasive technique that employs VOCs to diagnose and monitor therapy.[33] VOCs are metabolites that can be detected in human breath due to alveolar exchange.[34] This exchange allows expelled products to diffuse into inhaled air, rendering EBA an efficacious alternative to invasive procedures such as blood test analysis.[31]

Spiking Neural Network

Recent studies have revealed that bio-inspired artificial olfaction could be the solution to long-standing issues in handling multivariate data, computing and power demands, low accuracy, and significant delays in processing and categorising scents. One promising approach involves encoding multivariate data into temporal signatures, which can be utilised for target gas detection in rank-order-based olfactory systems. However, traditional pattern-matching methods and unpredictable spike shuffles may impede the system's effectiveness. To counter this, a neuromorphic hardware system has been proposed for massively parallel and low-power processing of incoming rank-order patterns. This system can classify continuous data with up to 96.5% accuracy while using only a fraction of the whole pattern frame and can also detect abnormalities in rank-order patterns caused by sensor array drift. It operates in real-time, making it a highly effective solution.[35]

ENOSE

The smart electronic nose (E-nose) has seen rapid application growth in a variety of industries in recent years. The performance of E-nose is mostly determined by the recognition algorithm in addition to sensor arrays. This article introduces the response signal characteristic of a sensor before focusing on the E-nose's signal processing. The algorithms are then split into traditional and artificial neural networks (ANNs)-based categories based on differences in how features are processed.[36]

Over the past few decades, a range of conventional pattern recognition methods, such as discriminant function analysis (DFA), principal component analysis (PCA), and cluster analysis (CA), have been created and applied to gas recognition.[37,38] These techniques are known for their versatility and their ability to effectively process small datasets. Moreover, certain conventional pattern recognition algorithms continue to be widely used for their clear, straightforward approach and low computational requirements.

Recent advancements in ANN techniques, particularly in the realms of computer vision and time series, have opened up new avenues of possibility within the field of E-nose.[39] Empirical evidence has demonstrated the heightened effectiveness and noise-resistance of ANN over traditional approaches when dealing with large datasets, allowing for expedient and accurate recognition, a crucial component for practical applications. In order to glean feature information pertaining to distinct gases, a number of technologies have been implemented within E-nose research, such as multilayer perceptron (MLP), convolutional neural network (CNN), gated recurrent unit (GRU), and long short-term memory (LSTM).[40-44]

VOCs as Biomarkers

The pathophysiological mechanisms underlying various disease states can have a significant impact on the production of VOCs, resulting in changes to the exhaled VOC profile, or volatolome.[45-48] Various factors can contribute to these changes, including inflammation, oxidative stress, anaerobic conditions, enzymatic activity, bacteria, and microbiome populations.[49] Exhaled VSCs, linked to bacterial activity and produced by local microbial-enzymatic breakdown of amino acids and other mechanisms, have been suggested as potential biomarkers for the diagnosis and monitoring of halitosis.[50,51] Extensive research demonstrates that halitosis can be identified and correlated with various oral diseases, with mouth-hosted microorganisms contributing to breath malodour.[52-54] An intriguing finding by Morris and Read suggested that at least 7% of the participants had halitosis that was resistant to oral hygiene and conventional management strategies, leading them to hypothesise that in these situations, halitosis might not be caused by an oral disease or condition but rather originate from a distant source.[55] Later, Tonzetich and Johnson[56] measured the volatile reducing substances (VRSs) and investigated the chemical makeup of the pooled saliva from halitosis patients. VRSs are created in the oral cavity during halitosis, with primarily VSCs, particularly MM and H2S, being identified, according to their industrial process to assess odour strength. Since then, numerous scientific studies have established the existence of detectable exhaled VSCs and their potential as noninvasive biomarkers for the diagnosis and monitoring of halitosis, utilising state-of-the-art technologies, including chromatography, spectrometry, and various chemical gas sensors.

Recent Trends

OdoriFy

Identifying odorant molecules for human Odorant receptors (ORs), whether wild-type or mutant, can be a complex process. However, with the help of OdoriFy, a web server equipped with deep neural network (DNN)-based prediction engines, this task becomes significantly more manageable. OdoriFy is designed to classify user-supplied chemicals as either odorants or nonodorants, and subsequently identify responsive ORs for a given query odorant. Following this, validation of the interaction between the odorant and OR is conducted through odorant-OR pair analysis. Overall, the innovative capabilities of OdoriFy offer a promising approach to enhancing our understanding of OR function and odour perception.[57] The system utilises explainable AI, providing a rationale for each of its predictions. In addition, OdoriFy is founded upon an extensive collection of hand-selected data on human ORs, offering information on both known agonists and nonagonists, making it highly interactive and resource-rich.[58]

Halimeter

Methyl mercaptan (MM) is the primary source of oral malodour, while hydrogen sulfide (H2S) is the gas that the Halimeter detects with the greatest sensitivity. The Halimeter is a useful tool for predicting oral malodour due to its strong correlation with H2S and MM [Figure 2].[59]

OralChroma

The OralChromaTM is a remarkable tool that can detect the absolute amounts of dimethyl sulfide, hydrogen sulfide, and methyl mercaptan in less than 10 min, making it a valuable asset in the diagnosis and monitoring of oral halitosis. It can differentiate between the primary three VSCs linked to halitosis and is remarkably accurate even at low concentrations. However, it is important to note that it is an expensive device and may contaminate the sample with impurities.[60]

Olfactory Perception

The DREAM Olfaction Prediction Challenge endeavours to forecast human olfactory perception for 19 semantic descriptors pertaining to odour, strength, and pleasantness, leveraging chemical characteristics and machine learning models, in view of recent research linking odorant physicochemical qualities to olfactory perceptions.[61,62] Through a comprehensive virtual screening approach, this methodological framework can unearth novel structural motifs for ligands. The relationship between chemical structure and odour has been explored through the use of advanced DNN, graph neural networks (GNN), or CNN.[63-65]

NONINVASIVE DIAGNOSIS

Photometric Sensors

Lagopati *et al*. have developed a highly efficient photometric detection method for VOCs, which are biomarkers for lung cancer (LC) detection.[66] The use of metalloporphyrins modified gold nanorods (AuNRs) as nanosensors has significantly improved the sensor's stability and performance by preventing the device from deteriorating, as proposed by Zhong *et al*.[67] In a clinical study carried out by Sun *et al*.,[68] it is crucial to design nanosensors that can bind VOCs more strongly than Van der Waals forces. The precision and sensitivity of the sensor application can be enhanced by utilising chemically sensitive dyes, such as porphyrin, to construct colourimetric arrays with a low limit of detection (LOD) of parts per billion (ppb), which can be used for LC detection. These findings suggest that the use of nanomaterial-based sensors could be a promising approach for detecting and diagnosing LC, highlighting the importance of further research in this area.

Electrochemical Sensors

According to research by Homayoonnia and Zeinali[69] (2016), Metal-Organic Framework (MOF) nanoparticles (NPs) are a reliable sensor for detecting VOCs. Obermeier *et al*.,[70] concluded in their study by stating that capacitive sensors that use NPs as a dielectric layer have been successful in detecting acetone, methanol, ethanol, and isopropanol concentrations. Yang *et al*. (2022) and Zhang *et al*. (2014) have both demonstrated that nanosensors exhibit high sensitivity at concentration levels, quick reaction times, linearity, and reversible reactions.[71,72]

Piezoelectric Sensors

In 2019, Haick *et al*. developed a sensor device that uses piezoelectric micro-cantilevers coated with a polymer to identify VOCs. The device is composed of eight micro-cantilevers and an electronic readout, and it can distinguish between different VOCs. However, the sensor's low cost means that more experimental work is needed to overcome its limitations. Future studies should aim to improve gas conveyance setups and test VOCs in water to observe how humidity affects VOC separation.[45]

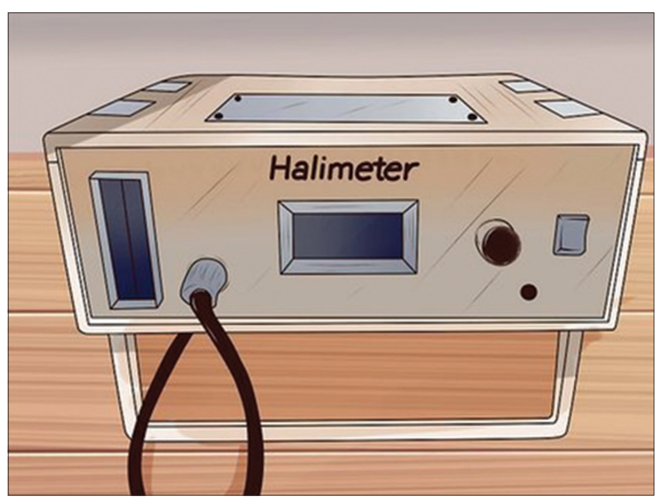

Figure 2: The figure depicts the schematic representation of the Halimeter. Source: https://www.wikihow.life/Prevent-Bad-Breath

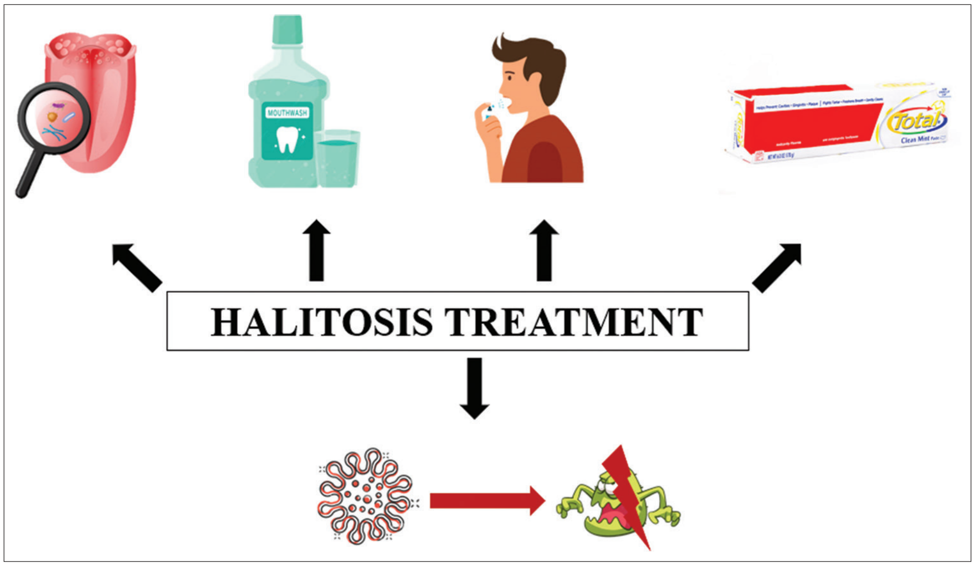

Figure 3: The figure depicts the treatment of halitosis. Reducing the microbial load, mouth rinses, breath freshener, Colgate total, and lethal photosensitisation

CLINICAL RELATION OF VSCS

Periodontal disorders can be a causative factor in the sudden development or exacerbation of halitosis due to the presence of germs in the oral cavity.[73] Infected sites provide a conducive environment for bacteria to settle down, multiply, and digest proteins, leading to an overabundance of VSCs in the oral cavity.[74,75] Due to the increased blood supply to these inflamed sites, the bacteria are seen to increase, leading to increased VSC production.[76] This increase is related to gingival bleeding and >3 mm pocket depth in periodontal patients, as observed in a quantitative exhaled breath study by Rosenberg *et al*.,[77] using gas chromatography/mass spectrometry (GC/MS). In a case report by Moore *et al*., it is stated that patients presenting with periodontitis are characterised by halitosis and heavy tongue coating.[78,79] Improper or unsatisfactory dental hygiene and other systemic diseases lead to halitosis, which is a niche for the growing bacteria, was reported in a study carried out by Vandekerckhove B *et al*.[80] and Zhou *et al*.,[81] in their research works, have shown that the concentrations of exhaled VSC in people with periodontitis were higher and linked with the presence of *Prevotella intermedia, P. gingivalis*, and *Bacteroides forsythus*. In conditions such as gingivitis, periodontitis, xerostomia, mucosal ulcerations, and deep dental lesions, increased production of VSCs adds to the presence or severity of halitosis.[82] These noninvasive diagnostic methods for oral halitosis could be used in distinguishing exhaled and inhaled VSCs and also in monitoring their levels.

TREATMENT TRENDS IN HALITOSIS

Role of Bacterial Load in Halitosis

The objective of the study by Grover *et al*., was to investigate the effectiveness of short-term antimicrobial mouth rinses and tongue debridement in reducing the bacterial load on the tongue, which is a crucial factor contributing to the development of malodorous breath.[5,83]

Tongue Coating and Malodour Treated with Periodontal Therapy

In addition, the study by Van Steenberghe *et al*.,[84] aimed to assess the impact of periodontal treatment on specific oral malodour parameters over 6 months. However, the study findings by Lee and Hong revealed that, even when combined with a mouth rinse, periodontal treatment, including tongue scraping, did not significantly alter the microbial load of the tongue or VSC levels in patients with intermediate periodontitis.[85,86]

Oral Care Flavours

Bradshaw *et al*., in their study, investigated the potential of flavours to inhibit bacterial production of offensive chemicals, particularly gram-negative bacteria. The researchers developed a quantitative *in vitro* technique to identify H2S generation by *Klebsiella pneumoniae*. They assessed the ability of the Quest dental flavour palette to reduce H2S generation and created a database of taste component effects. The Quest Breath Freshness Panel then evaluated the most effective tastes. These findings have led to the development of breath-freshening flavours incorporated into various oral care products, such as toothpaste, mouthwash, chewing gum, and breath films, through the utilisation of the *in vitro* VSC-inhibition technique.[87,88]

Colgate Total

In the early 1990s, Colgate Total was developed as a groundbreaking toothpaste with the aim of combating various oral health issues such as plaque, gingivitis, calculus, tooth decay, and halitosis. This innovative technique combined the antimicrobial triclosan with a copolymer of polyvinyl methyl ether and maleic acid (PVM/MA) as well as sodium fluoride (TCF) to achieve optimal oral retention and sustained release. As a result, the buildup of tooth plaque and bad breath was significantly reduced, and oral bacteria could be effectively controlled for longer periods of time. Furthermore, regular use of the product was found to decrease the incidence of tartar and progressive coronal caries. A new triclosan/copolymer/fluoride toothpaste variation has been recently introduced that features a mouth-freshening taste and provides prolonged control of bad breath for up to 12 h. The long-term retention and release of triclosan in the TCF formula is attributed to the copolymer, which offers protection against these common oral health issues.[89,90]

Lethal Photosensitisation of Oral Pathogens

A study conducted by Krespi *et al*. (2005) and Williams and Ummins (2005) revealed that lethal photosensitisation of two common oral pathogens can be achieved through the use of high-intensity red-filtered halogen lamps and diluted methylene blue. This suggests that the use of laser or light energy in combination with photosensitising agents could be a promising treatment option for antibiotic resistance.[90,91]

Tonsilloliths

A study by Levin and Rosenberg evaluated the prevalence of self-reported bad breath among Israeli army recruits and how it correlated with other self-reported metrics and overall oral health. The study involved 426 young adult volunteers, mostly male, between the ages of 18 and 19, who were divided into three groups based on their oral health. The results revealed that 8.2% of the participants had unpleasant breath and taste, while 33.3% were heavy smokers. In addition, 7.3% of the individuals reported tonsilloliths, and 18.8% reported gingival haemorrhage. The research indicated a significant association between self-reported bad breath and unpleasant taste, gingival bleeding, and overall dental health. This study was the first to report that approximately one in every thirteen young adults may have tonsilloliths [Figure 3].[85,92]

CONCLUSION

Halitosis, a common condition that can significantly impact quality of life, requires precise diagnosis and treatment. A multidisciplinary approach is necessary for prevention, diagnosis, and management. Dental professionals should be familiar with halitosis as it can indicate oral or systemic disease. Our review focuses on the potential use of AI olfaction in halitosis detection. While commercially available VSCs assessment systems are helpful, they may not be effective for extra-oral halitosis. An artificially intelligent olfaction system could provide a noninvasive and low-cost solution for identifying both oral and extra-oral halitosis, with great sensitivity to both VSCs and VOCs patterns. This system could also identify the distant systemic source of the malodour.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Vijayalakshmi R, Mahendra J, NalinaKumari C B, Ravi N, Ramani S. Artificial intelligence in periodontics-An overview. IP Int J Periodontol Implantol 2023;8:71-4.
2. Ding H, Wu J, Zhao W, Matinlinna JP, Burrow MF, Tsoi JKH. y. Front Dent Med 2023;4. doi: 10.3389/fdmed. 2023.1085251.
3. Artificial Intelligence: A neoteric reach in Periodontics. Available from: https://www.jptcp.com/index.php/jptcp/article/view/2651. [Last accessed on 2023 Oct 16].
4. Khounganian RM, Alasmari ON, Aldosari MM, Alghanemi NM. Causes and management of halitosis: A narrative review. Cureus 2023;15:e43742.
5. Bicak DA. A current approach to halitosis and oral malodor- A mini review. Open Dent J 2018;12:322-30.
6. Yaegaki K, Coil JM. Examination, classification, and treatment of halitosis; clinical perspectives. J Can Dent Assoc 2000;66:257-61.
7. Wu J, Cannon RD, Ji P, Farella M, Mei L. Halitosis: Prevalence, risk factors, sources, measurement and treatment-A review of the literature. Aust Dent J 2020;65:4-11.
8. Tangerman A, Winkel EG. Extra-oral halitosis: An overview. J Breath Res 2010;4:017003. doi: 10.1088/1752-7155/4/1/017003.
9. Sparkes AC. Ethnography and the senses: Challenges and possibilities. Qual Res Sport Exerc 2009;1:21-35.
10. Joussain P, Digard B, Luneau L, Djordjevic J. Individual differences in verbal and non-verbal affective responses to smells: Influence of odor label across cultures. Chem Senses 2017;42:37-46.
11. Sarafoleanu C, Mella C, Georgescu M, Perederco C. The importance of the olfactory sense in the human behavior and evolution. J Med Life 2009;2:196-8.
12. Sorokowska A, Schriever VA, Gudziol V, Hummel C, Hähner A, Iannilli E, *et al*. Changes of olfactory abilities in relation to age: Odor identification in more than 1400 people aged 4 to 80 years. Eur Arch Otorhinolaryngol 2015;272:1937-44.
13. Laing DG, Legha PK, Jinks AL, Hutchinson I. Relationship between molecular structure, concentration and odor qualities of oxygenated aliphatic molecules. Chem Senses 2003;28:57-69.
14. Poivet E, Tahirova N, Peterlin Z, Xu L, Zou DJ, Acree T, *et al*. Functional odor classification through a medicinal chemistry approach. Sci Adv 2018;4:eaao6086. doi: 10.1126/sciadv.aao6086.
15. de Gennaro G, Farella G, Marzocca A, Mazzone A, Tutino M. Indoor

and outdoor monitoring of volatile organic compounds in school buildings: Indicators based on health risk assessment to single out critical issues. Int J Environ Res Public Health 2013;10:6273-91.
16. Herrmann A. The Chemistry and Biology of Volatiles. John Wiley and Sons; Geneva (Switzerland): 2011.
17. Genva M, Kenne Kemene T, Deleu M, Lins L, Fauconnier ML. Is it possible to predict the odor of a molecule on the basis of its structure? Int J Mol Sci 2019;20:3018. doi: 10.3390/ijms20123018.
18. Tripathy S, Mathur A, Mehta V. Revolutionizing Oral Cancer Screening: New Approaches and Emerging Technologies. Asian Pacific Journal of Cancer Prevention. 2023;24:4007-8. doi:10.31557/APJCP.2023.24.12.4007.
19. Nara K, Saraiva LR, Ye X, Buck LB. A large-scale analysis of odor coding in the olfactory epithelium. J Neurosci 2011;31:9179-91.
20. Hampelska K, Jaworska MM, Babalska ZŁ, Karpiński TM. The role of oral microbiota in intra-oral halitosis. J Clin Med Res 2020;9:2484. doi: 10.3390/jcm9082484.
21. Zhang Y, Zhu C, Cao G, Zhan J, Feng X, Chen X. Dynamic alterations of oral microbiota related to halitosis in preschool children. Front Cell Infect Microbiol 2021;11:599467. doi: 10.3389/fcimb. 2021.599467.
22. Porter SR, Scully C. Oral malodour (halitosis). BMJ 2006;333:632-5.
23. Aydin M, Harvey-Woodworth CN. Halitosis: A new definition and classification. Br Dent J 2014;217:E1.
24. Rani H, Ueno M, Zaitsu T, Furukawa S, Kawaguchi Y. Factors associated with clinical and perceived oral malodor among dental students. J Med Dent Sci 2015;62:33-41.
25. Ehizele AO, Ojehanon PI. Relationship between the concentration of volatile sulphur compound and periodontal disease severity in Nigerian young adults. Niger Med J 2013;54:149-52.
26. Bokhari SAH, Khan AA, Butt AK, Azhar M, Hanif M, Izhar M, *et al*. Non-surgical periodontal therapy reduces coronary heart disease risk markers: A randomized controlled trial. J Clin Periodontol 2012;39:1065-74.
27. Johnson RA, Wichern DW. Applied Multivariate Statistical Analysis. Pearson; New Jersey, USA; 2019.
28. Pennazza G, Marchetti E, Santonico M, Mantini G, Mummolo S, Marzo G, *et al*. Application of a quartz microbalance based gas sensor array for the study of halitosis. J Breath Res 2008;2:017009. doi: 10.1088/1752-7155/2/1/017009.
29. Belizário JE, Faintuch J, Malpartida MG. Breath biopsy and discovery of exclusive volatile organic compounds for diagnosis of infectious diseases. Front Cell Infect Microbiol 2020;10:564194. doi: 10.3389/fcimb. 2020.564194.
30. Farrugia G, Szurszewski JH. Carbon monoxide, hydrogen sulfide, and nitric oxide as signaling molecules in the gastrointestinal tract. Gastroenterology 2014;147:303-13.
31. Dharmawardana N, Goddard T, Woods C, Watson DI, Ooi EH, Yazbeck R. Development of a non-invasive exhaled breath test for the diagnosis of head and neck cancer. Br J Cancer 2020;123:1775-81.
32. Das S, Pal S, Mitra M. Significance of exhaled breath test in clinical diagnosis: A special focus on the detection of diabetes mellitus. J Med Biol Eng 2016;36:605-24.
33. Bhandari MP, Veliks V, Stonāns I, Padilla M, Šuba O, Svare A, *et al*. Breath sensor technology for the use in mechanical lung ventilation equipment for monitoring critically ill patients. Diagnostics (Basel) 2022;12:430. doi: 10.3390/diagnostics12020430.
34. Broza YY, Haick H. Nanomaterial-based sensors for detection of disease by volatile organic compounds. Nanomedicine 2013;8:785-806.
35. Vanarse A, Osseiran A, Rassau A. Real-time classification of multivariate olfaction data using spiking neural networks. Sensors 2019;19:1841. Doi: 10.3390/s19081841.
36. Yamada Y, Takahashi Y, Konishi K, Katsuumi I. Association of odor from infected root canal analyzed by an electronic nose with isolated bacteria. J Endod 2007;33:1106-9.
37. Nakamura M, Sugimoto I, Kuwano H, Lemos R. Chemical sensing by analysing dynamics of plasma polymer film-coated sensors. Sens Actuators B Chem 1994;20:231-7.
38. Gardner JW, Shurmer HV, Tan TT. Application of an electronic nose to the discrimination of coffees. Sens Actuators B Chem 1992;6:71-5.
39. Han JK, Kang M, Jeong J, Cho I, Yu JM, Yoon KJ, *et al*. Artificial olfactory neuron for an in-sensor neuromorphic nose. Adv Sci 2022;9:e2106017. doi: 10.1002/advs. 202106017.
40. Kang M, Cho I, Park J, Jeong J, Lee K, Lee B, *et al*. High accuracy real-time multi-gas identification by a batch-uniform gas sensor array and deep learning algorithm. ACS Sens 2022;7:430-40.
41. Li M, Liu H, Chang J, Dai T, Nagashima K, Deng Z, *et al*. Quantitatively discriminating alcohol molecules by thermally modulating NiO-based sensor arrays. Adv Mater Technol 2022;7:2100762.
42. Huang GB, Zhu QY, Siew CK. Extreme learning machine: A new learning scheme of feedforward neural networks. In: 2004 IEEE International Joint Conference on Neural Networks (IEEE Cat. No. 04CH37541), IEEE, 2005. Available from: http://ieeexplore.ieee.org/document/1380068/.
43. Peng P, Zhao X, Pan X, Ye W. Gas classification using deep convolutional neural networks. Sensors 2018;18. doi: 10.3390/s18010157.
44. Bengio Y, Simard P, Frasconi P. Learning long-term dependencies with gradient descent is difficult. IEEE Trans Neural Netw 1994;5:157-66.
45. Haick H, Broza YY, Mochalski P, Ruzsanyi V, Amann A. Assessment, origin, and implementation of breath volatile cancer markers. Chem Soc Rev 2014;43:1423-49.
46. Hakim M, Broza YY, Barash O, Peled N, Phillips M, Amann A, *et al*. Volatile organic compounds of lung cancer and possible biochemical pathways. Chem Rev 2012;112:5949-66.
47. Nakhleh MK, Haick H, Humbert M, Cohen-Kaminsky S. Volatolomics of breath as an emerging frontier in pulmonary arterial hypertension. Eur Respir J 2017;49:1601897. doi: 10.1183/13993003.01897-2016.
48. Nakhleh MK, Quatredeniers M, Haick H. Detection of halitosis in breath: Between the past, present, and future. Oral Dis 2018;24:685-95.
49. Sharma A, Kumar R, Varadwaj P. Smelling the disease: Diagnostic potential of breath analysis. Mol Diagn Ther 2023;27:321-47.
50. Avincsal MO, Altundag A, Ulusoy S, Dinc ME, Dalgic A, Topak M. Halitosis associated volatile sulphur compound levels in patients with laryngopharyngeal reflux. Eur Arch Otorhinolaryngol 2016;273:1515-20.
51. Aydin M, Bollen CML, Özen ME. Diagnostic value of halitosis examination methods. Compend Contin Educ Dent 2016;37:174-8;quiz180.
52. Amann A, Corradi M, Mazzone P, Mutti A. Lung cancer biomarkers in exhaled breath. Expert Rev Mol Diagn 2011;11:207-17.
53. Barash O, Peled N, Hirsch FR, Haick H. Sniffing the unique "odor print" of non-small-cell lung cancer with gold nanoparticles. Small 2009;5:2618-24.
54. Baumbach JI, Maddula S, Sommerwerck U, Besa V, Kurth I, Bödeker B, *et al*. Significant different volatile biomarker during bronchoscopic ion mobility spectrometry investigation of patients suffering lung carcinoma. Int J Ion Mobil Spectrom 2011;14:159-66.
55. Morris PP, Read RR. Halitosis; variations in mouth and total breath odor intensity resulting from prophylaxis and antisepsis. J Dent Res 1949;28:324-33.
56. Tonzetich J, Johnson PW. Chemical analysis of thiol, disulphide and total sulphur content of human saliva. Arch Oral Biol 1977;22:125-31.
57. Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, *et al*. The Cellular basis of loss of smell in 2019-nCoV-infected individuals. Brief Bioinform 2021;22:873-81.
58. Gupta R, Mittal A, Agrawal V, Gupta S, Gupta K, Jain RR, *et al*. OdoriFy: A conglomerate of artificial intelligence-driven prediction engines for olfactory decoding. J Biol Chem 2021;297:100956. doi: 10.1016/j.jbc. 2021.100956.
59. Winkel EG, Tangerman A. O5 Clinical association of volatile sulfur compounds, Halimeter values, organoleptic score and tongue coating in oral malodor. Oral Dis 2005;11:99.

60. Yoshihara A, Sato M, Miyazaki H. O11 Effect of oral health care on the recovery from surgery in elderly patients by measuring volatile sulphur compounds. Oral Dis 2005;11:101.
61. Keller A, Vosshall LB. Olfactory perception of chemically diverse molecules. BMC Neurosci 2016;17:55.
62. Keller A, Gerkin RC, Guan Y, Dhurandhar A, Turu G, Szalai B, *et al*. Predicting human olfactory perception from chemical features of odor molecules. Science 2017;355:820-6.
63. Achebouche R, Tromelin A, Audouze K, Taboureau O. Application of artificial intelligence to decode the relationships between smell, olfactory receptors and small molecules. Sci Rep 2022;12:18817.
64. Ilyas N, Shahzad A, Kim K. Convolutional-neural network-based image crowd counting: Review, categorization, analysis, and performance evaluation. Sensors 2019;20:43. doi: 10.3390/s20010043.
65. Tripathy S, Mathur A, Mehta V. A View of Neural Networks in Artificial Intelligence in Oral Pathology. Oral Surg. doi: https://doi.org/10.1111/ors.12848.
66. Lagopati N, Valamvanos TF, Proutsou V, Karachalios K, Pippa N, Gatou MA, *et al*. The role of nano-sensors in breath analysis for early and non-invasive disease diagnosis. Chemosensors 2023;11:317. doi: 10.3390/chemosensors11060317.
67. Tripathy S, Mathur A, Mehta V. A view of neural networks in artificial intelligence in oral pathology. Oral Surg [Internet]. 2023; doi: 10.1111/ors.12848.
68. Sun J, Lu Y, He L, Pang J, Yang F, Liu Y. Colorimetric sensor array based on gold nanoparticles: Design principles and recent advances. Trends Analyt Chem 2020;122:115754. doi: 10.1016/j.trac. 2019.115754.
69. Homayoonnia S, Zeinali S. Design and fabrication of capacitive nanosensor based on MOF nanoparticles as sensing layer for VOCs detection. Sens Actuators B Chem 2016;237:776-86.
70. Obermeier J, Trefz P, Wex K, Sabel B, Schubert JK, Miekisch W. Electrochemical sensor system for breath analysis of aldehydes, CO and NO. J Breath Res 2015;9:016008. doi: 10.1088/1752-7155/9/1/016008.
71. Yang X, Chi H, Tian Y, Li T, Wang Y. Research progress of graphene and its derivatives towards exhaled breath analysis. Biosensors 2022;12:48. doi: 10.3390/bios12020048.
72. Zhang Y, Gao G, Liu H, Fu H, Fan J, Wang K, *et al*. Identification of volatile biomarkers of gastric cancer cells and ultrasensitive electrochemical detection based on sensing interface of Au-Ag alloy coated MWCNTs. Theranostics 2014;4:154-62.
73. Loesche WJ, Kazor C. Microbiology and treatment of halitosis. Periodontol 2000 2002;28:256-79.
74. Bollen CML, Beikler T. Halitosis: The multidisciplinary approach. Int J Oral Sci 2012;4:55-63.
75. Awano S, Gohara K, Kurihara E, Ansai T, Takehara T. The relationship between the presence of periodontopathogenic bacteria in saliva and halitosis. Int Dent J 2002;52(Suppl 3):212-6.
76. Yaegaki K, Sanada K. Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease. J Periodontal Res 1992;27:233-8.
77. Rosenberg M, Kulkarni GV, Bosy A, McCulloch CA. Reproducibility and sensitivity of oral malodor measurements with a portable sulphide monitor. J Dent Res 1991;70:1436-40.
78. Moore WE, Holdeman LV, Cato EP, Smibert RM, Burmeister JA, Palcanis KG, *et al*. Comparative bacteriology of juvenile periodontitis. Infect Immun 1985;48:507-19.
79. Simonson LG, Goodman CH, Bial JJ, Morton HE. Quantitative relationship of Treponema denticola to severity of periodontal disease. Infect Immun 1988;56:726-8.
80. Vandekerckhove B, Van den Velde S, De Smit M, Dadamio J, Teughels W, Van Tornout M, *et al*. Clinical reliability of non-organoleptic oral malodour measurements. J Clin Periodontol 2009;36:964-9.
81. Zhou H, McCombs GB, Darby ML, Marinak K. Sulphur by-product: The relationship between volatile sulphur compounds and dental plaque-induced gingivitis. J Contemp Dent Pract 2004;5:27-39.
82. Tsai CC, Chou HH, Wu TL, Yang YH, Ho KY, Wu YM, *et al*. The levels of volatile sulfur compounds in mouth air from patients with chronic periodontitis. J Periodontal Res 2008;43:186-93.
83. Grover HS, Blaggana A, Jain Y, Saini N. Detection and measurement of oral malodor in chronic periodontitis patients and its correlation with levels of select oral anaerobes in subgingival plaque. Contemp Clin Dent 2015;6(Suppl 1):S181-7.
84. Van Steenberghe D, Zhao H, Soers C, Pauwels M, Quirynen M. O8 Impact of periodontal therapy (including antiseptics) on tongue coating and malodour. Oral Dis 2005;11:100.
85. Nonaka A, Tanaka M, Anguri H, Nagata H, Kita J, Shizukuishi S. P25 Clinical assessment of oral malodor intensity expressed as absolute value using electronic nose. Oral Dis 2005;11:114.
86. Lee YH, Hong JY. Oral microbiome as a co-mediator of halitosis and periodontitis: A narrative review. Front Oral Health 2023;4:1229145. doi: 10.3389/froh. 2023.1229145.
87. Bradshaw DJ, Perring KD, Cawkill PM, Provan AF, McNulty DA, Saint EJ, *et al*. Creation of oral care flavours to deliver breath-freshening benefits. Oral Dis 2005;11(Suppl 1):75-9.
88. Virdi, M. Emerging Trends in Oral Health Sciences and Dentistry. BoD – Books on Demand; 2015.
89. Williams MI, Cummins D. The technology behind Colgate Total Advanced Fresh. Compend Contin Educ Dent 2003;24 (9 Suppl):4-9; quiz 42.
90. Williams M, Ummins DC. O10 The technology behind Colgate® TotalTM toothpaste. Oral Dis 2005;11:101.
91. Krespi YP, Slatkine M, Marchenko M, Protic J. Lethal photosensitization of oral pathogens via red-filtered halogen lamp. Oral Dis 2005;11(Suppl 1):92-5.
92. Levin L, Rosenberg M. P1 Bad breath among young Israeli recruits. Oral Dis 2005;11:106.