

# Are Gram Negative Microbes Producing Odoriferous Compounds Friends or Foes to Humans?

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ABSTRACT

Gram negative microorganisms produce volatile sulphur compounds widely implicated in the production of malodour and destruction of various human tissues. However, the volatile sulphur compounds have also been found to be beneficial in the regulation of many processes in the human system. It is important to have a good knowledge of the effect the volatile sulphur compounds on human tissues, especially since a number of treatment protocols for the management of oral malodour have been hinged on the reduction in the concentration of these odoriferous gases. This review is therefore to outline how much of a friend or foe the odoriferous volatile sulphur compounds, produced by oral microbials, are to humans.

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## INTRODUCTION

Halitosis, a noticeable unpleasant odour that emanates from the mouth, has been reported to be objectionable to others (Odai et al., 2011) It raises a lot of concerns among sufferers and is a common reason for dentists' consultation. This is because it negatively impacts on patients' daily activities such as communication, self-confidence and self-esteem, social and intimate relationships such as dating and marriage as well as employability and career aspirations (Yanagisawa et al., 2005; Azodo et al., 2010; Azodo et al., 2011). A number of gram-negative organisms produce many gases which have been implicated in the production of oral malodour (Kotti & Subramanyam, 2015).

The classification of halitosis by Yaegaki & Coil (2000) includes categories of genuine halitosis, pseudo-halitosis and halitophobia with genuine halitosis subclassified as physiologic halitosis or pathologic halitosis. Whereas individuals with genuine malodour from intraoral causes and pseudo-halitosis may improve after tongue cleaning and dental treatments such as mechanical plaque control, restoration of carious lesions, removal of grossly carious teeth, removal of impacted teeth, excision of fistula and drainage of discharging sinuses (Ehizele & Akhionbare, 2013;

Omoriegbe & Akpata, 2013), patient with halitophobia may remain delusional after dental management and therefore benefit from carefully planned psychological evaluation and management (Uguru et al., 2011; Akpata

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& Omoriegbe, 2016).

The burden of oral malodour is real and may precipitate psychological and social effects on the afflicted individuals. Therefore, many management protocols, including the elimination of potentially odoriferous compounds, have been proposed (Porter and Scully, 2006; Veerasha et al., 2011; Rösing & Loesche, 2011). These various groups of odoriferous compounds include; i) Volatile Sulphur Compounds (VSC): hydrogen sulphide, methyl mercaptan, dimethyl sulphide, ii) Volatile Aromatic Compounds and Amines (VACA): indole, skatole, pyridine, picoline, urea, ammonia, methylamine, dimethylamine, putrescine, cadaverine, iii) Short and Medium- Chain Fatty Acids or Organic Acids: propionic acid, butyric acid, valeric acid, isovaleric acid, esanoic acid); iv) Alcohols: methanol, ethanol, propanol, v) Volatile Aliphatic Compounds:

cyclopropane, cyclobutene, pentane, vi) Aldehydes and Ketones (acetaldehyde, acetone, benzophenone, acetophenone). (Milella, 2015; Audrain, 2015)

Intraoral production of potentially odoriferous compounds starts with the breakdown of food protein, intracellular polypeptide chains in dental plaque as well as desquamated epithelial cells in the oral mucosa and periodontal pockets (Palmer, 2014; Reddy, 2017; Kriebel et al., 2018). Protein in the diet, saliva and gingival fluid are converted to peptides and then to sulphur containing amino acids by bacterial and host proteases (Brosnan & Brosnan, 2006; Kaman et al., 2012). These sulphur containing amino acids are finally converted to highly volatile odoriferous compounds through asaccharolytic catabolism of the anaerobic gram negative organisms which can be; Gram negative cocci that are facultative anaerobes (*Neisseria* spp); Gram negative cocci that are obligate anaerobes (*Veillonella parvula*); Gram negative rods and filaments that are facultative anaerobes (*Haemophilus* spp, *Eikenella Corrodens*, *Aggregatibacter actinomycetem comitans*, *Capnocytophaga* spp); Gram negative rods and filaments that are obligate anaerobes (*Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Seimonas sputigena*, *Leptotrichia buccalis*, *Treponema denticola*) (Brosnan & Brosnan, 2006; Palmer, 2014)

Whereas it is not in doubt that the products of these organisms may produce various types of offensive odour which can instantly reach and offend those in the immediate environment because of their volatile nature, it is a truism that odoriferous compounds may also play beneficial roles in the human systems and contribute immensely to the general wellbeing of humans. This review is to outline how much of a friend or foe the odoriferous and volatile sulphur compounds, produced by oral microbials, are to humans.

### Hydrogen sulphide

Krespi *et al.* (2006) reported that bacteria like *Peptostreptococcus anaerobius*, *Micros prevotti*, *Eubacterium limosum*, *Bacteroides* spp, *Centipedia periodontii* and *Selenomonas artermidis* produce Hydrogen sulphide (H<sub>2</sub>S) from cysteine while *Prevotella intermedia*, *Prevotella loescheii*, *Porphyromonas gingivalis*, and *Treponema denticola* produce H<sub>2</sub>S from serum and this plays an important role in oral malodour. At a concentration of 0.00047, half of the human population can perceive H<sub>2</sub>S as an offensive odour similar to sewage or rotten egg (Power, 2004). Hydrogen sulphide (H<sub>2</sub>S) is also produced by the enzymatic activity of L- cysteine sulfhydrase on the proteinogenic amino acid L-cysteine (Elsej et al., 2010; Yoshida et al., 2010). The enzymatic reaction that produces H<sub>2</sub>S also produces other volatile aromatic compounds and amines, such as pyruvate and ammonia (Audrain, 2015). It has been documented that H<sub>2</sub>S can be synthesized in mammalian tissues from L-cysteine and L-homocysteine in

enzymatic reactions that require cystathionine beta-synthase (CBS), cystathionine gamma-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST) as catalysts (Tomasova et al., 2016). H<sub>2</sub>S is also produced in the colon of mammals by gut bacteria with other odoriferous gases (methane, NO and CO) short-chain fatty acids, alcohols, aldehydes, amines (trimethylamine) and aromatic derivatives of amino acids (phenols, cresols, indoles) (Tomasova et al., 2016). H<sub>2</sub>S is the third gas transmitter next to nitrous oxide (NO) and carbon monoxide (CO) (Köhn et al., 2012; Farrugia & Szurszewski, 2014).

A wide range of biological effects are associated with H<sub>2</sub>S, including improved reperfusion in trauma and circulatory shock (Szabo, 2007; Szabo, 2017), retardation of cardiac hypertrophy through its anti-fibrotic property (Shen et al., 2015), anti-hypertensive effects through vasorelaxation and suppression of vascular inflammation (Pan et al., 2017). Furthermore, it has been shown that H<sub>2</sub>S regulates tumor angiogenesis via the modulation of vascular endothelial growth factor (VEGF) and activation of phosphatidylinositol-3-kinase (PI3K) and mitogen activated protein kinases (MAPK) (Papapetropoulos et al., 2009; Köhn et al., 2012). H<sub>2</sub>S plays important roles in angiogenesis and in regulation of ageing and apoptosis (Pal et al., 2018). Hydrogen sulphide has also been reported to be a major cytoprotectant and redox modulator with many potentially therapeutic effects (Pal et al., 2018). Physiologically, H<sub>2</sub>S exerts beneficial effects on the gastrointestinal, neuronal, cardiovascular, respiratory, renal, and hepatic systems (Pal et al., 2018). However, in diabetes mellitus, H<sub>2</sub>S can be described as a double-edged sword as its overproduction has been linked with pathogenesis of  $\beta$ -cell death in diabetes while its deficiency, due to its increased consumption by hyperglycemic cells, has been suggested to be the cause of diabetic endothelial dysfunction, nephropathy, and cardiomyopathy (Szabo, 2012).

### Methyl mercaptan

Methyl mercaptan is also known as methanethiol (CH<sub>3</sub>S) and is commonly referred to as the 'the essence of skunk gas' (National Center for Biotechnology Information, 2019). It is a natural substance found in the blood, brain, other animal tissues as well as plant tissues, in certain foods, such as nuts, cheese, onions, radishes and asparagus (Clark, 2018). L- Methionine released into the saliva and the gingival crevicular fluid after degradation of food protein and undergoes enzymatic reaction with L- methionine  $\alpha$ - deamino- $\gamma$ - mercaptomethane-lyase to produce methyl mercaptan,  $\alpha$ -Ketobutyrate and ammonia (Yoshimura et al., 2000). According to Krespi et al. (2006), *Fusobacterium nucleatum*, *Fusobacterium periodonticum*, *Eubacterium* spp and *Bacteroides* spp produce methyl mercaptan from methionine while *Porphyromonas gingivalis*, *Treponema denticola*,

*Porphyromonas endodontalis* will produce methyl mercaptan from serum.

Methyl mercaptan is a colourless gas perceived as rotten cabbage, burnt rubber or stagnant water and therefore one of the main compounds responsible for oral malodour and the smell of flatus (O'Neil, 2016; Lewis, 2007).

It has been reported that methyl mercaptan in humans binds to protein and erythrocytes, stabilizing erythrocyte membranes against hypotonic hemolysis (Bingham et al., 2001; National Center for Biotechnology Information, 2019). It gets majorly into the respiratory system by inhalation and is then directly translocated to the vascular system. (Bingham et al., 2001). Acute inhalation of methyl mercaptan has been reported to cause serious adverse effects. Although skin and eye absorption are minimal, there may be eye and mucous membrane irritation (Bingham et al., 2001). There may also be other dose related clinical signs such as hyperactivity, tachypnea, cyanosis, muscular weakness, convulsions, respiratory and central nervous system depression as well as skeletal muscular paralysis (Bingham et al., 2001).

### **Dimethyl sulphide**

Dimethyl sulphide is the third volatile sulphur compound implicated in oral malodour (Tangerman & Winkel, 2013; Nani et al, 2017). It is produced naturally by bacterial transformation of dimethyl sulfoxide (DMSO) (Libury et al., 2016). It gives an offensive smell like cooked vegetables such as maize, cabbage, beetroot and seafoods, canned tomatoes and malt contaminated by bacteria (Dolan, 2010).

The benefit of dimethyl sulphide in cell protection and prevention of ageing has been documented (Guan et al., 2017). It plays an important role in Methionine (Met) sulfoxide reductase A- catalytic antioxidation and reacts with reactive oxygen species thereby reducing oxidative stress, protecting cells and preventing ageing (Bin et al., 2017; Guan et al., 2017). The concentration of dimethyl sulphide in mammalian tissue was reported to decreased after aging (Guan et al., 2017).

The precursor of dimethyl sulphide (dimethyl sulfoxide) has been reported to be useful in the treatment of skin diseases because it penetrates the skin and membranes optimally and aids transportation of small molecules through the skin. (Capriotti & Capriotti, 2012). Dimethyl sulfoxide has been used to treat Scleroderma and chemotherapy extravasations characterized by tingling, burning, pain, swelling, redness of chemotherapy injection site and eventual tissue death if untreated (Bowman, 2016). Although there is inconclusive evidence that it may also be helpful in the treatment of Alzheimer's disease and arthritis, care must be taken in its use because of the risk of permitting other harmful substances into the skin and causing damage to human eye (Bowman, 2016).

### **CONCLUSION**

The effects of the volatile sulphur compounds are largely dependent on their concentration in the different human tissues. These effects can both be detrimental or beneficial. VSC will play varying roles in processes, such as production of oral malodour, periodontal tissue breakdown, regulation of human systems and prevention of ageing/ apoptosis, to varying degrees in different individuals. It is therefore important to carry out future research work to objectively determine the level at which VSC is desirable and at what point it becomes dangerous in the various human systems. This knowledge will be especially valuable in the treatment of oral malodour which may involve the reduction of the concentration of these odoriferous gases.

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