Saliva as Diagnostic Medium to Detect Infectious Disease in Human Body: A Review

Dian Yosi Arinawati(✉) and Mitha Novianti

Universitas Muhammadiyah Yogyakarta, Special Region of Yogyakarta 55183, Kasihan, Indonesia
dianyosi@umy.ac.id

Abstract. Saliva is a oral biological fluid that has many benefits and has an function for maintaining oral health and can be clinically informative as a diagnostic media. Biomarkers in saliva are molecules that contain certain ingredients can be used to diagnose disease or assess the development and outcome of treatment. The characteristics of biomarkers make it feasible to be an alternative diagnostic media. The latest emerging technology has revealed medically that salivary biomarkers are important for detection many disease conditions such as cancer, viruses, bacteria, cardiac disease, autoimmune and metabolism disturbance. The purpose of this study is to determine the role of saliva as a diagnostic medium through its various biomarkers in saliva that can detect diseases caused by viral, bacterial and fungal infections in the body. This literature review of PubMed database was conducted without any limitation on date of publication to identify the potential of saliva as diagnostic medium of infectious diseases. Saliva has potential as medium diagnostic for ZIKA virus in the early week of symptom onset. High level of IgG can be detected in saliva of Helicobacter pylori bacterial infection in the body. Changes in salivary proteins such as calprotectin and histatin also have important diagnostic values in the detection of fungal infections. It can be concluded that saliva has potential as diagnostic medium that can be used in detecting various diseases caused by viral, bacterial and fungal infections.

Keywords: bacterial · fungal · infection · saliva · viral

1 Introduction

According to World Health Organization (WHO) infectious diseases are diseases caused by microorganisms pathogens, including bacteria, parasites, viruses and fungi. The character of this disease is easy to spread to another person directly or indirectly (World Health Organization, 2020). The disease's transmission mode can be through food, vectors or air. Infectious diseases are formed when humans or animals as infectious agents are in an environment susceptible to infection by pathogenic microorganisms. The infectious agent can spread infection from one human to another, which can eventually cause disease (McArthur, 2019).

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In 2016, it was reported that the worldwide mortality rate was 56.9 million people, and more than half of them were caused by the top 10 diseases. Infectious diseases that were reported to be the deadliest worldwide in 2016 were lower respiratory tract infections. It is inversely proportional to the number of mortality due to tuberculosis and HIV/ AIDS which decreased compared to 2015.

Infectious diseases can be detected through laboratory tests. In the case of laboratory tests to detect Helicobacter pylori (H. Pylori) infection, it uses histology as the gold standard (Y.-K. Wang, 2015). Viral hepatitis is detected by urinalysis to check bilirubin levels as a basic evaluation. Diagnosis of acute hepatitis A can be done utilizing serological testing in blood to detect IgM antibodies hepatitis A virus (HAV). Additional testing is to detect viral RNA using RT-PCR (Lorio & John, 2021). HIV infection screening is carried out using Enzyme Immunoassays (EIA). In addition, Western blot is a method for detecting antibody characterization of each viral protein. This method is the gold standard as definitive confirmatory test for HIV (Huang et al., 2018). Some of the above examinations have weaknesses in diagnosing a disease. Limited facilities or services for hepatitis testing, low cost, and inadequate laboratory capacity, including rapid diagnostic tests (RDT) and virological tests, do not align with WHO guidelines (Easterbrook et al., 2017). Up to 7–14 day time consumption for Western Blot test in HIV patients and take costs money. In addition, this test is more expensive than the EIA test and can only be performed by a skilled person. EIA testing in HIV patients can also give false positive results, and the number and type vary with the test used. To overcome these weaknesses, it is necessary to have alternative diagnostic tests that are easy, inexpensive and have fast results (Huang et al., 2018).

Nowadays, saliva is widely used for medium diagnostic of systemic, dental, oral diseases and a person's physiological condition. Saliva is used as an alternative diagnosis as it is non-invasive, cheap, easy and can be done quickly and in bulk. Saliva contain of organic and inorganic components can be used as biological markers or biomarkers that provide clinical information (Califf, 2018). According to the National Institutes of Health (NIH), a biomarker is indicator taken from biological, pathogenic and pharmacological response to the therapeutic intervention that measured objectively. The progression and onset of the disease can be seen from concentration changes of the biomarker. Biomarkers are important to understand and evaluate to be useful in determining the presence, location and possibility of disease in a person's body. Many benefit of saliva as utilization for diagnosis, monitoring and diseases progression (Yoshizawa et al., 2013). For example, in psoriasis patient it was detection of high salivary K+ and alpha-amylase (sAA) values and low immunoglobulin A (IgA) are markers of H. pylori infection (Asa'ad et al., 2018). Furthermore, the analysis of various proteins and electrolyte ions in saliva can also be used to diagnose oral diseases and systemic diseases such as oral candidiasis, oral squamous cell carcinoma (OSCC), Sjögren's syndrome, breast cancer, and head and neck cancer (Kaczor-Urbanowicz et al., 2017).

Based on the above background, this literature review aims to determine the role of saliva as a diagnostic medium through various biomarkers that can detect diseases caused by viral, bacterial and fungal infections in the body.

2 Material and Method

Data search was carried out using literature study techniques by looking for sources or literature from international journals. The search for data sources was done without year restriction using the PubMed database. The inclusion criteria in this study were articles reporting topics related to saliva, diagnostic, and infectious disease, with no specific keywords and only written in English.

3 Discussion

Saliva is an oral biofluid that contains mostly water, electrolytes, and protein (Milioli et al., 2015). This biofluid has function to protect oral mucosal tissue from tooth erosion or demineralization and protection against pathogenic bacteria (Trindade et al., 2015). Saliva contains clinical information that is useful as an approach to prognostication, clinical or laboratory diagnosis with oral and systemic disease of the patient. Collected and stored saliva is easy and can be used for early diagnose of disease due to it contain specific biomarkers. The biomarkers contained in saliva make it has benefit for diagnostic media of point-of-care (POC), screening test and for clinical laboratory tests (Malamud, 2011).

3.1 Analysis of the Use of Saliva as a Diagnostic Medium

Saliva utilization of for diagnostic, monitoring and progression of disease is accurate and fast result, therefore improve the prognosis of the diasease (Roi et al., 2019). The salivary test has been viewed as a diagnostic medium with a wide area currently widely used. Salivary metabolism is a new advance in salivary diagnostics, that utilized metabolite present in saliva to detect various diseases (Malathi et al., 2014).

Saliva collection is not invasive and easy to collect therefore blood tests will be unnecessary if want to get similar or identical information. This condition is very important in several situations, such as patient pediatric, geriatric and or in remote area with a lack of medical personnel who draw blood from patients for various tests and laboratory procedures for blood collection. Oral tests using saliva to detect antibodies to HIV have been confirmed to have the same sensitivity and specificity as current blood tests. Saliva has ability to detect HIV antibodies, as similar reason it might be has potency to detect bacterial and fungal pathogens (Malamud, 2011). Saliva as a diagnostic medium has advantages: (1) Sample collection is easy and safe. Saliva sample collection is easier and safer than blood sample collection, especially in pediatric patients, anxious and less cooperative; (2) Saliva does not clot like blood. The use of saliva during diagnostic procedures is easier because it does not agglomerate to reduce manipulation during diagnostic procedures, (3) Non-invasive sample collection, (4) Correlation with blood levels, (5) Minimal cross-contamination risk, (6) Cost-effectiveness, and (7) Usability in mass screening test (Malathi et al., 2014; Pfaffe et al., 2011; Roi et al., 2019; Shah, 2018).

The limitation of diagnostic using saliva, including; (1) The level of markers in the saliva is not fully representative that can describe the level of markers in serum, (2)

the collection method and the level of salivary flow might influent the composition of saliva; (3) Salivary marker can be affected by salivary flow rate and salivary pH; (4) Even in different condition, the salivary flow rate among people is expected to be same; (5) Furthermore, composition of saliva can be affected by systemic condition such as consumptions of the drug; (6) Stability of biomarker in saliva might be affect by proteolytic enzyme come from oral cavity or microorganism, therefore some molecules can be degraded; (7) There is variation due to circadian rhythm; and (8) a sensitive detection system is required (Kaczor-Urbanowicz et al., 2017; Malamud, 2011; Mikkonen et al., 2016; Roi et al., 2019; Shah, 2018; Zhang et al., 2016).

Whole saliva is most often used to diagnose the systemic disease due to easy to collect and contains serum constituent. Salivary diagnostics can detect diseases/conditions caused by bacterial, viral and fungal infections by quantify antibodies, antigens or nucleic acid (Malathi et al., 2014). The following are some of the uses of saliva to diagnose various diseases caused by infectious pathogens.

3.2 Virus Infection

(a) Human Papillomavirus (HPV)

Oral diseases caused by viruses, the Human papillomavirus or HPV, are associated with oral cancer such as oral squamous cell carcinoma (OSCC). Chemical compounds found in the saliva of OSCC patients are protein markers such as M2BP, MRP14, CD 59, profilin 1 and catalase (Csősz et al., 2017; Shah, 2018). Salivary-specific protein levels such as CD44 expression as a cancer stem cell marker cytokeratin 19 (Cyfra 21–1), tissue polypeptide antigen (TPA), and cancer antigen 125 (CA-125) are increased in patients with OSCC and have been suggested to be used as a biomarker of oral cancer. The accuracy of detected OSCC reported about 81% using salivary micro-RNA, indicating the potential a saliva for detecting oral carcinomas (Sri Santosh et al., 2020). It was reported that salivary cortisol is increase in patient with OSCC, suggesting that it can be used for clinical marker stage of OSCC (Roi et al., 2019). Nucleic acid assay from saliva can be used for detection of HPV using polymerase chain reaction (PCR) method (Malamud, 2011).

(b) Human Immunodeficiency Virus (HIV)

Saliva has also been used successfully in diagnostic laboratories to detect HIV antigens and antibodies. Several diagnostic tests that can be used include quantitative reverse transcription polymerase chain reaction (qRT-PCR), ELISA, rapid tests, point-of-care (POC) and microfluidic diagnostic tools. In addition, HIV that neutralizes innate immune factors such as defensins has also been detected in saliva using advanced experimental methodologies such as liquid-chromatography-tandem mass spectrometry (Malamud, 2011).

(c) Hepatitis Virus

Salivary samples can detect anti-HAV (Hepatitis A Virus) antibodies and the HAV genome. Antibodies to hepatitis A virus can be detected by salivary IgM. Antibodies of patients infected with hepatitis A can be detected during the first 90 days after diagnosis.

Salivary testing of hepatitis A virus is correlated with the serum method (Amado Leon et al., 2015).

(d) SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quickly spread around the world. It was reported first time in Wuhan City, Hubei Province, China. This virus cause a disease commonly referred to as Covid-19, can be transmitted person-to person directly through saliva of infected person (Singhal, 2020; Wang et al., 2020).

SARS-CoV-2 has been recognized belong to the same family Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in the 21st century (Li et al., 2020; Sri Santosh et al., 2020). The transmission mode of this virus can be direct from infected human to another human or indirectly through contamination object in fomites from droplets infected person (Sri Santosh et al., 2020).

Swabbing from nasopharyngeal and analysis using RT-qPCR is the golden standard for detecting SARS-CoV-2 (Czumbel et al., 2020). The RT-qPCR assay is easier to validate and is more recommended for diagnostic purposes (Han & Ivanovski, 2020).

Several studies have stated that saliva can be a medium to detect SARS-CoV-2. The salivary collection that is easy, non-invasive and can be done outside the laboratory is an alternative option in diagnosing SARS-CoV-2. Saliva sample in alternative medium for some who feel uncomfortable doing a nasopharyngeal swab. It was reported that the sensitivity and specificity of saliva and swabbing from nasopharyngeal in detecting SARS-CoV-2 by RT-qPCR showed no significant difference (Czumbel et al., 2020; Vaz et al., 2020).

Apart from viral load testing with RT-qPCR, several other tests that can be selected, such as the ELISA test to detect salivary IgM/IgG associated with SARS-CoV-2 infection, SARS-CoV-2 double-membrane extracellular vesicles (EVs), protein anti-SARS-CoV-2 surface, viral load titers, EVs-derived CD4 + T/CD8 + cells, and pro-inflammatory cytokines can be potential diagnostic and prognostic biomarkers for SARS-CoV-2 infectious disease (Han & Ivanovski, 2020).

During tissue damage, Lactic acid dehydrogenase, or LDH, is released with lung damage in SARS-CoV-2 patients. The higher the viral load in the saliva is, the higher the LDH level in the blood will be. Saliva can be used as a diagnostic medium in detecting SAR-CoV-2 as it can provide the same information as serum levels in the blood related to viral load in saliva and LDH levels in patients infected with SARS-CoV-2 (Azzi et al., 2020).

(e) Zika Virus

Zika virus or ZIKV is a flavivirus, a family of viruses that can cause several diseases such as yellow fever, dengue fever, West Nile, and Japanese encephalitis (Khurshid et al., 2019; Plourde & Bloch, 2016). Zika can cause Zika fever, which is caused by the Zika virus, spread through mosquito bites (Khurshid et al., 2019).

In the initially, ZIKV only detected in serum and cerebrospinal fluid. Over time, Zika virus detection focuses on biofluid in our body, including urine, saliva and tissue, for diagnostic testing. Serological analysis and detection of ZIKV IgM and IgG antibodies

still require further research. Low viremia and cross-reactivity with other flaviviruses lead to a high probability of false positive results. Currently, the RT-PCR assay is considered a sensitive diagnostic test with high specificity (Khurshid et al., 2019).

Saliva has the potential as an early diagnostic medium for ZIKV in the first week of symptom onset. The excretion of viral RNA in urine and saliva was observed up to 29 days after symptom onset with a higher viral load than in blood (Yong et al., 2018).

Utilization of saliva as diagnostic tools provide simple, efficient analysis for diagnosting of ZIKV. It can be challenging for studying point-of-care technology (Yong et al., 2018).

3.3 Bacterial Infection

(a) Psoriasis

Psoriasis is disease with have symptom like erythematous papules and plaque cause by autoimmune etiology. Predisposing factors in psoriasis include genetics, smoking, deficiency of vitamin D, drinking alcohol and overweight. Genetic factors are the most influential predisposition to the development of psoriasis (Yong et al., 2018).

Evidence suggests that infection can trigger the development of psoriasis by binding superantigens to T cell receptors and the major histocompatibility complex (MHC) system expressed on antigen-presenting cells and ultimately activates CD4 + T cells. H. pylori infection is suspected as one of the most common microbial infections that can worsen psoriasis. Increased H. pylori infection in psoriasis patients was demonstrated by the presence of H. pylori IgG detected in the ELISA assay. Several studies have revealed that other diagnostic tests, namely urea breath or stool antigen testing, cannot show an increased prevalence of active H.pylori infection in psoriasis patients (Yong et al., 2018). Onsun et al. and Campanati et al. showed that H. pylori infection in psoriasis patients had higher Psoriasis Area and Severity Index (PASI) scores (Campanati et al., 2015; Onsun et al., 2012). Changes in saliva composition in psoriasis patients include a decrease in IgA and an increase in C-reactive protein (CRP), haptoglobin, K+, alpha-amylase (sAA), tumor necrosis factor (TNF-α), monocyte chemoattractant protein (MCP-1), IL –1β.

Changing in saliva composition such as Sodium (Na+), potassium (K+), chloride (Cl−), and alpha-amylase (sAA) is reported has correlation with severity of psoriasis (Asa'ad et al., 2018). Higher level of salivary IL1β, TNF-, TGF-, and MCP-1 was reported in psoriasis patient (Asa'ad et al., 2018; Martina et al., 2020). In can be suggested that saliva can be used for diagnostic and monitoring in psoriasis disease (Martina et al., 2020).

(b) Pielonefritis

Pyelonephritis is a disease in the form of inflammation of the excretory system (urinary tract) caused by infection with Escherichia coli (E. coli) bacteria. Initially Pyelonephritis diagnosis is made by urine analysis. The use of analysis from dipstick urinalysis is insufficient to show the state of individual reactivity to pathological processes of the excretory system. Dipstick urinalysis, as a conventional diagnostic method, is often associated with false positive and false negative results, so in determining the pathological process, it is necessary to carry out other diagnostic tests (Angelova et al., 2019).

(c) Gastritis

Saliva is a very useful medium in detecting digestive system disorders. The level of acidity or pH and reducing Na+ ions in saliva can be higher risk for gastroesophageal reflux. Therefore, maintaining the esophagus condition can be obtained by controlling salivary pH. Helicobacter pylori is one of the bacteria that causes digestive system diseases. These tiny bacteria are reported as causal factor for peptic ulcers and gastritis. High level of immunoglobulin G in serum was reported has correlation with H. pylori infection. The DNA of this bacteria can be detected in saliva using PCR or ELISA with a sensitivity of 85% (Woźniak et al., 2019).

(d) Tuberculosis

Recent studies have shown that the saliva biomarker is 6 times higher than in serum samples from tuberculosis (TB) patients. Salivary biomarkers can be useful for diagnosing TB disease and as a monitoring medium for treatment response. Research by Phalane et al. showed an increase in the expression of IL-1β and IL-13 in the saliva of tuberculosis (TB) patients. IL-1β is a major salivary marker that can be used in diagnosing TB. Immunological tests to diagnose TB disease can be more useful, especially in situations with limited resources. Immunological tests can be performed as screening tests at the point of care or on a point-of-care basis which can be performed outside the laboratory. This simple test can support the use of easily available samples such as saliva from TB52 patients (Jacobs et al., 2016).

3.4 Fungal Infection

Oral candidiasis is fungal infection caused by Candida albicans and its commonly appeared in oral cavity of person with bad oral hygiene and medico-compromised condition. Clinically there are many forms, namely pseudomembranous (acute/chronic), erythematous (acute/chronic), plaque (chronic), and nodular (chronic). Several other studies have shown an association between oral candidiasis and a history of diabetes mellitus, Sjögren's syndrome, a combination of chronic renal failure and hemodialysis. Various methods can isolate Candida from the oral cavity, including smears, plain swabs, imprint cultures or trace cultures, whole saliva collection, concentrated oral rinses, and mucosal biopsies. The concentrated oral rinses method is one of the most suitable techniques for determining the concentration of Candida in the oral cavity. However, this method is inadequate for detecting the Candida infection site. Although it cannot detect a localized site of infection, this method allows the quantitation of microbes other than Candida species. The concentrated rinse method is also easy to perform and more sensitive than the trace culture technique (Tooyama et al., 2015).

Analysis of the number of fungi in saliva provides valuable information in cases of oral candidiasis. Changes in salivary protein can be a marker in detecting fungal infections in the body. Salivary proteins that have diagnostic value include immunoglobulins, Hsp70, calprotectin, histatin, mucin, proline-rich proteins (PRPs), and peroxidase (Malathi et al., 2014). Patients with Sjögren's syndrome with oral candidiasis show elevated salivary calprotectin levels. This increase may be due to mucosal transudation of the inflamed mucosa. A clinical study evaluating histatin-5 production showed

a significant decrease in saliva in HIV-positive individuals with an increase in candida colonization (Vila et al., 2019).

Patients with different disorders of the salivary glands are known to have a high predisposition to oral candidiasis. Some of them are caused by impaired defenses in the body or the host (Vila et al., 2019). Altered differential expression of various proteins, including immunoglobulin G antibodies in denture stomatitis, suggests an important role of innate immunity in determining how the host responds to inflammation associated with denture stomatitis (Khiyani et al., 2019).

4 Conclusion

Saliva is a hypotonic fluid that contains most of water and some inorganic components in the form of electrolytes and organic components in oral cavity. In addition to maintaining the balance of oral health, saliva can also be used as a medium for diagnosing various systemic diseases. One of the advantages of saliva is that it can be collected and stored easily so that it can be used as an alternative diagnostic medium for the detection of a disease, such as detecting infections in the body, namely viral, bacterial and fungal infections.

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