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Effectiveness of Cetylpyridinium Chloride in Reducing the Growth of Bacteria that Cause Periodontal Disease

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Abstract: Periodontal disease is a common dental and oral health problem in the community which is usually caused by *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Streptococcus mutans*. This study aimed to provide information about the cetylpyridinium chloride (CPC) which can inhibit the growth of bacteria that cause periodontal disease. This was a narrative review literature study sourced from Google Scholar, Science Direct, and Pubmed (MEDLINE) databases. The keywords used were CPC inhibition, antimicrobial agent, periodontal pathogen bacteria, periodontal disease, and mouthwash. The results obtained 31 articles with appropriate titles and three review articles. Cetylpyridinium chloride is a mouthwash containing a monocationic quaternary ammonium compound consisting of quaternary nitrogen with a positive charge. with a positive charge. The molecular formula of CPC was C12H38CIN, and the molecular weight was 340g/mol with the IUPAC name 1-hexadecylpyridinium chloride. Cetylpyridinium chloride could inhibit the growth of oral pathogenic bacteria by adsorbing negative charges from bacteria, increasing the permeability of bacterial cell walls, decreasing cell metabolism, damaging cell membranes, and reducing the attachment of bacteria to the tooth surface which could reduce the growth of bacterial cells as the cause of periodontal disease. In conclusion, cetylpyridinium chloride is a potent antibacterial agent suitable used as a mouthwash to prevent periodontal disease.
Keywords: cetylpyridinium chloride inhibition; antimicrobial agent; periodontal pathogen bacteria; periodontal disease; mouthwash

INTRODUCTION

Periodontal disease is a common dental and oral health problem in the community. Data of RISKESDAS (*Riset Kesehatan Dasar*) 2018 showed that the prevalence of periodontitis in Indonesia was quite high at 74.1%.[1] Based on the results of data analysis of the Global Burden of Disease Study in 1990-2010, it was reported that severe periodontitis (severe periodontitis) was the 6th most common condition in the world, affecting 743 million people with a prevalence ranging from 11.2%.[2,3]

In general, periodontal disease often affects the periodontal tissues such as the gingiva, cementum, periodontal ligament, and alveolar bone. The first stage of periodontal disease is called gingivitis triggered by the formation of plaque on the teeth. This plaque will affect the gums, so, the gums look swollen and reddish. If left untreated, gingivitis can progress to periodontitis, which causes the bones and tissues that support these teeth to deteriorate.[3]

The pathogenesis of periodontal disease is influenced by the interaction between host factors and bacteria usually dominated by *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*.[4] These bacteria will express various virulent factors, such as lipopolysaccharide (LPS), gingipain, fimbriae/pili, collagenase, (erythrocyte) lectins, capsules, proteases, and superoxide dismutase which play an important role in the development of the early stages of periodontitis and release toxic and damaging metabolites.[5,6]

Prevention of periodontal disease can be done and controlled properly through dental treatment using several other alternatives easy to be used such as mouthwash as an antimicrobial agent.[2,7] Mouthwash is considered effective as an early method of preventing caries and periodontitis due to its ability to reach places that are difficult to clean with a toothbrush and dental floss.[7,8]

Cetylpyridinium chloride (CPC) is one of the active components of mouthwash as a pharmacological antimicrobial from the cationic quartenary ammonium (QA) biocide compound with a broad spectrum which provides a bactericidal effect.[9,10] CPC concentrations of 0.05%-0.1% are effective as antimicrobials. However, CPC concentrations above 0.1% can have a toxic effect on humans. Moreover, the ability of CPC as an antimicrobial agent will be less effective if below these concentrations.[11,12] The use of CPC as an ingredient in mouthwash is considered safe and effective as an antibacterial agent and does not provide serious side effects, so, that it can be an alternative to prevent periodontal disease.[11,12,13] Therefore, this review article aimed to provide some information about the mouthwash containing CPC in inhibition the growth of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* bacteria that causes periodontal disease.

METHODS

This was a narrative literature review study sourced from Google Scholar, Science Direct, and Pubmed (MEDLINE) databases. The strategy used in data collection was in the form of writing keywords used to find articles to be reviewed with a publication period between 2013-2022 (Table 1). The keywords used were CPC inhibition, antimicrobial agent, periodontal patogen bacteria, periodontal disease, mouthwash.

RESULTS

The identification results from searching in Google Scholar, Science Direct, and Pubmed (MEDLINE) in which the title contained one or more keywords obtained 25 articles with appropriate titles and three review articles. There were six Indonesian journal articles and 22 international journal articles. The next step was process of screening the search result data to obtain data types that had similarities in the research theme. The eligibility stage was carried out to determine which articles fulfilled the inclusion and exclusion criteria based on the suitability of the title and content of the article. The next stage was a search with inclusion criteria, namely articles with a time limit of the last ten years that had been set by the author in the form of studies related to the topic. At this stage, 10 articles were obtained in accordance with the topics discussed.

Table 1. Tracking scientific articles

No	Keywords	Years	Databases	Number of articles found
1	CPC inhibition	2013 - 2022	Google Scholar	7800
			Science Direct	318
			Pubmed	424
2	Antimicrobial agent		Google Scholar	8800
			Science Direct	433
			Pubmed	219
3	Periodontal pathogen bacteria		Google Scholar	400
			Science Direct	40
			Pubmed	676
4	Periodontal disease		Google Scholar	400
			Science Direct	720
			Pubmed	909
5	Mouthwash		Google Scholar	5.100
			Science Direct	516
			Pubmed	988

DISCUSSION

Dental and oral health is one of the important factors in supporting the health of the body. The business of society in the current era of globalization has an impact on the neglect of dental and oral health. Neglected oral and dental health can lead to periodontal disease caused by dental plaque.[14]

Periodontal disease is a collection of inflammatory conditions of the supporting tissues of the teeth which is caused by bacteria. The cause of periodontal disease lies in a cumulative process, the consequences of which can be calculated from the size and the duration of plaque accumulation. This disease is universal and is the most common public health problem after caries.[15] Periodontal disease generally often affects the periodontal tissues such as the gingiva, cementum, periodontal ligament, and alveolar bone. The first stage of periodontal disease is called gingivitis. Gingivitis is triggered by the formation of plaque on the teeth. Plaque will affect the gums, so the gums look swollen and reddish. If left untreated, gingivitis can progress to periodontitis, which causes the bones and tissues that support these teeth to deteriorate.[3] Plaque control can be done chemically with the use of mouthwash.[8] To prevent this disease, plaque control can also be done by providing motivation to always maintain oral hygiene, scaling, polishing teeth, how to use a toothbrush, using dental floss and mouthwash correctly.[14]

There are two types of bacteria discussed in this article. *Porphyromonas gingivalis* is a Gram-negative, non-motile, asaccharolytic bacterium, is an obligate anaerobic, rod-shaped 0.5-2 m long, does not form spores, and on solid media for blood to form colonies that appear smooth (sometimes rough), shiny, convex shape, 1-2 mm in diameter, and black pigmented colonies.[16] When grown on blood agar surfaces, the colonies are initially white to cream in color. Name *Porphyromonas* It comes from the Greek adjective porphyreos meaning purple and the Greek noun monas meaning unit. Therefore, the word *Porphyromonas* means porphyrin cell because the colonies on the blood agar plate darken from the edges towards the center and turn dark red to black over 4-8 days due to the accumulation of protohemes.[6] *Aggregatibacter actinomycetemcomitans* is a Gram-negative, non-motile anaerobic coccobacillus that is predominantly found in patients with aggressive periodontitis. These bacteria colonize the oral cavity as normal flora. These bacteria attack the periodontal tissue and interfere with the body's immune defense system.[17] The new *Aggregatibacter actinomycetemcomitans* isolated from the human oral cavity, always piled and small (±1mm), rough

surface, translucent colonies, with star-shaped internal morphology.[18]

Oral pathogenic bacteria have the ability to express and release various virulence factors, one of which is leukotoxin.[19] Leukotoxins are proteins that are part of the RTX (Repeats in Toxin) toxin that helps bacteria to outwit the host's immune response during infection. The main targets of leukotoxins are PMN cells, monocytes, T lymphocytes, and human macrophages.[20] The role of leukotoxins in cell death is by way of necrosis and apoptosis.[18] Pathogenic bacteria will also form colonies in the subgingival cleft and cause damage to the periodontal tissue due to its virulence factors, such as adhesins, fimbriae, exotoxins, and endotoxins.[6]

The induction and progression of periodontal tissue destruction is a complex process involving plaque accumulation, release of bacterial substances, and a host inflammatory response.[6] Lipopolysaccharide (LPS) contributes to the pathogenesis of periodontal disease, namely the process of alveolar bone resorption, through the activation of osteoclasts. LPS is well known for its toxicity and ability to cause unwanted host inflammation.[21] By inducing the production of proinflammatory cytokines, lipopolysaccharide from gram-negative periodontal bacteria, primarily *P. gingivalis,* can activate IL-1beta gene transcription by Th1 cells. Because Th1 cell activity suppresses Th2 antibacterial immunity, the Th1 response elicited by lipopolysaccharide could be part of a periodontopathic bacteria's immune evasion strategy in order to survive in a hostile environment. In contrast, the Th1 immune response may aid in the management of *Porphyromonas gingivalis* infection within cells.[22]

Cetylpyridinium chloride is a mouthwash containing a monocationic quaternary ammonium compound consisting of quaternary nitrogen with a positive charge. CPC has the molecular formula C12H38CIN, and a molecular weight of 340g/mol with the IUPAC name 1-hexadecylpyridinium chloride.[23] The presence of this positive charge will facilitate binding to the negative cell membrane of the microbe and destroy cell integrity which causes leakage of cell components.[11] CPC is soluble in water, alcohol, chloroform, benzene and ether. Due to its solubility properties, CPC can be prepared in alcohol-free preparations.[8] Cetylpyridinium chloride also has anti-bacterial, anti-plaque and could treat gingivitis. After two weeks of continuous use the condition of the oral cavity will improve.[8] In a previous study on the effectiveness of mouthwash containing CPC through clinical trials conducted by Rawlinson et al[23] showed that two mouthwashes containing CPC with concentrations of 0.05% and 0.1% could inhibit plaque growth clinically and statistics and did not show a significant difference between the two of them.

The decrease in plaque accumulation by pathogenic oral bacteria is influenced by the use of non-alcoholic mouthwashes such as Cetylpyridinium chloride (CPC), which is a broad-spectrum antimicrobial and has bactericidal properties similar to Chlorhexidine mouthwash.[19] Mouthwash containing CPC if used diligently will has the ability to adsorb negative charges from bacteria, increase the permeability of bacterial cell walls, decrease cell metabolism, damage lipid membranes so that bacterial cell membranes will rupture and leakage of cell components that cause cell death, reduce bacterial attachment to tooth surfaces, and inhibit bacterial cell growth.[8]

The CPC mouthwash is widely sold in the market due to its antimicrobial ability. In mouthwash, the effective concentration of CPC ranges from 0.05% to 0.1% but the most commonly used is 0.07% CPC. This CPC 0.07% has an acceptable minimum inhibitory concentration (MIC), so that concentration is the best choice as an antimicrobial in most available CPC mouthwashes. Its effective concentration is in the range of 0.05% to 0.1%. Above these concentrations it can be toxic to humans and cannot be used as a therapeutic agent. While below that concentration it becomes less effective against microbes to control oral pathogens. At this concentration, this mouthwash containing CPC without alcohol can be used every day, it will not be toxic if it does not exceed the recommended concentration.[11,24,25,26] Research by Schaeffer et al[27] proved that CPC 0.075% with 0.05% alcohol-free sodium fluoride had antibacterial activity against *S. mutans* of >99.9%. Sreenivasan et al[12] and He et al[26] stated that 0.075% alcohol-free CPC could reduce bacteria 35.3% during the first 12 hours of use and 70.9% after 14 days of use. Sreenivasan et al[12] conducted a study on the antimicrobial effect of CPC on 19 oral micro-

organisms, and the results showed a decrease in supragingival plaque bacteria by CPC, namely >90%. However, the results also showed that chlorhexidine was more effective in inhibiting supragingival plaque bacteria by >98% than alcohol-free 0.05% CPC with 90% antibacterial activity. Kang et al[28] conducted a study of CPC, ZnCl2, and CPC+ZnCl2 on five strains tested, namely *S. aureus, S. mutans, P. gingivalis, P. intermedia,* and *T. forsythia*. The results showed that CPC and ZnCl2 effectively inhibited the growth of almost all bacteria. However, ZnCl2 was more effective than CPC to suppress bacterial growth, but it was not significant. While CPC+ZnCl2 showed the greatest activity in inhibiting bacterial growth. According to the results of this study, the antibacterial activity of each sample showed the same pattern in five bacterial strains of *S. aureus, S. mutans, P. gingivalis, P. intermedia,* and *T. forsythia*. However, *P gingivalis* showed a different pattern, namely the inhibition by ZnCl2 had a significant difference compared to CPC and the combination of CPC+ZnCl2. But the inhibitory effect between CPC and the combination of CPC+ZnCl2 showed a statistically not significant difference.[28]

Chlorhexidine has indeed become the gold standard of mouthwash, but long-term use of chlorhexidine can cause discoloration of teeth and tongue, parageusia, as well as irritation and hypersensitivity reactions to the oral mucosa. Based on research, mouthwash containing CPC without alcohol is safe to use every day and for a long time.[25] The CPC can be a better and more effective alternative to help reducing the number of bacteria that cause plaque and periodontal disease and eliminate the occurrence of gingivitis and halitosis.[11]

CONCLUSION

Cetylpyridinium chloride can inhibit the growth of oral pathogenic bacteria by adsorbing negative charges from bacteria, increasing the permeability of bacterial cell walls, decreasing cell metabolism, damaging cell membranes, and reducing the attachment of bacteria to the tooth surface which can reduce the growth of bacterial cells as the cause of periodontal disease.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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