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Effectiveness of Using *Weissella cibaria* CMU Bacteria as Oral Probiotics for Halitosis Therapy: A Scoping Review

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ABSTRACT

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Halitosis is an unpleasant odor that is produced during exhalation, originating both inside and outside the oral cavity with volatile sulphur compound (VSC) as the main component. VSC is produced as a result of protein degradation by gram-negative anaerobic pathogenic bacteria. Halitosis poses a problem in the field of dentistry and has an impact on the psychosocial well-being of patients. Current halitosis therapy through conventional mechanical and chemotherapeutic methods still has obstacles, so it is necessary to look for alternative therapies that are safer and more effective, including through the use of *Weissella cibaria* CMU bacteria as an oral probiotic. Clinical investigations on humans have provided just a small amount of data on the efficacy of *Weissella cibaria* CMU as an oral probiotic for the treatment of halitosis. Purpose of this article to analyze the effectiveness of *Weissella cibaria* CMU as an oral probiotic for halitosis therapy from various human clinical studies. Preferred Reporting Item Guidelines for Methods of Systematic Review and Meta Analysis (PRISMA) selection process for articles. The articles were sourced from PubMed, Google Scholar and ResearchGate databases for the period 2013-2023 using the Boolean search "halitosis" AND "oral probiotics" AND "*Weissella cibaria*." The inclusion and exclusion criteria were used for a total of 4 articles, which were then reviewed. Clinical studies have shown that *Weissella cibaria* CMU can be used as an oral probiotic to improve halitosis. It is also safe for the body and health, thus it may be considered of as a support option for halitosis therapy.

KEYWORDS:

Halitosis, volatile sulphur compound (VSC), oral probiotics, *Weissella cibaria* CMU

INTRODUCTION

Halitosis, malodor, fetor oris atau bad breath are terms that generally describe a foul or unpleasant odor during exhalation. This can come from either inside or outside of the mouth cavity.^{1,2,3,4} Types of halitosis according to Miyazaki H et al cited by Hunny Sharma in 2015⁴ are classified into physiological halitosis, pathological halitosis (intra oral and extra oral), pseudohalitosis and halitophobia. Almost 90% of halitosis cases have an etiology that originates from intraoral factors.⁵ The source of intra oral halitosis can be due to the presence of periodontitis, gingivitis, periodontal pocket, deep caries, endodontic lesions, pericoronitis, mucosal ulceration, periimplant disease, oral malignancy, food debris trapped in

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the oral cavity, tongue debris, poor oral hygiene, restorations with insufficient dexterity, and factors that cause a decrease in salivary flow rate.^{6,7,8} Extra oral halitosis is halitosis whose source is related to conditions in the ear, nose, throat, pathological conditions of the lungs, gastrointestinal tract and halitosis through the bloodstream (blood borne halitosis which is usually related to endocrine diseases, metabolic disorders, liver disease and certain drugs and foods) which are carried to the lungs and then evaporate when entering the exhalation.⁹ According to Lanton P et al cited by Sharma H et al in 2015⁴ they state that certain medications that can cause halitosis because it reduces salivary flow, namely antidepressants, decongestants, narcotics, antipsychotics, antihistamines and antihypertensives. Behavior and habits of consuming alcohol and tobacco that causes the mouth to dry out, can also increase the risk of halitosis.⁷ Since the oral environment is dynamic, the balance of the normal flora (commensal) of the oral cavity, which prevents the colonization of pathogenic bacteria, is the key element that contributes to the development of halitosis, despite the fact

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that it can be brought on by a variety of factors.^{10,11}

Halitosis not only causes problems in the field of dentistry, according to Heo HY et al cited by Lee DS et al¹² it can also have an impact on the quality of life of sufferers because it causes problems with social interaction, decreased self-confidence, and mental stress. The component that causes halitosis which generally originates from within the oral cavity is Volatile Sulfur Compound (VCS) which is a product of the decomposition of sulfur-containing amino acids by gram-negative anaerobic pathogenic bacteria in the oral cavity, especially on the tongue's dorsal surface.⁴ The prevalence of halitosis from research in several countries ranges from 14.8-75.1%.^{13,14,15,16}

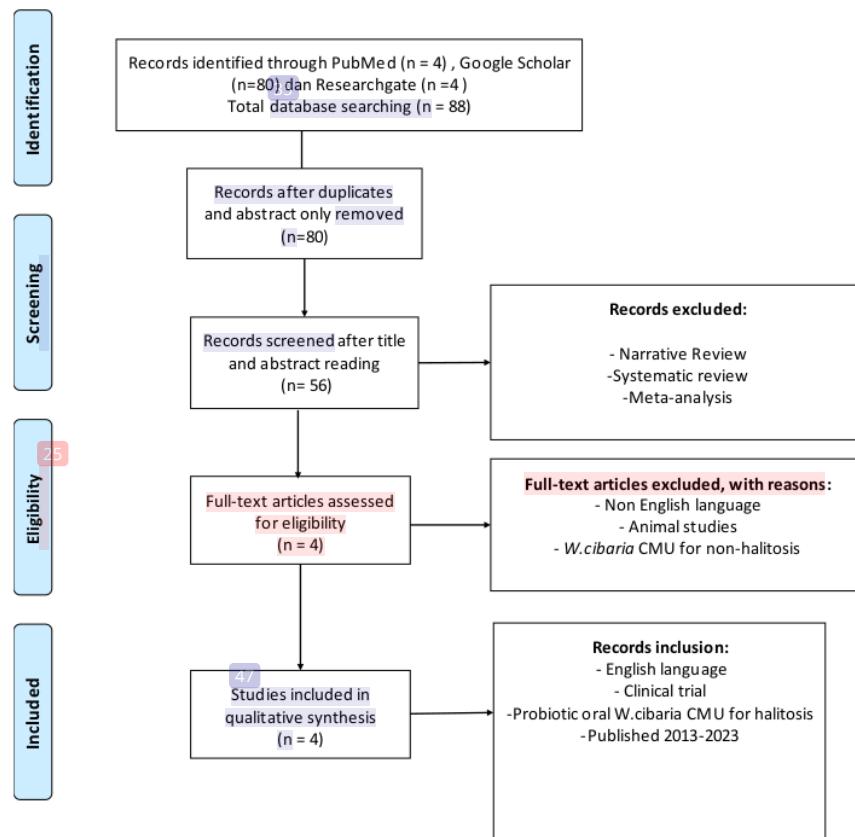
Halitosis management has been commonly carried out so far to eliminate pathogenic bacteria that causes halitosis and maintain oral hygiene, it's done through conventional mechanical methods (brushing teeth, using dental floss, using a tongue scrapper, scaling, and root planning) and chemotherapeutic methods (mouthwash, toothpaste, mouth spray).^{4,7,17,18} However, there are still weaknesses in these methods related to the risk of negative impacts on microflora homeostasis in the oral cavity, bacterial resistance, trauma to the tongue and short duration of effectiveness, so it is necessary to find alternative strategies for halitosis management that are safer and more effective.¹⁹ The oral probiotic method is currently being developed as an alternative effort for halitosis therapy.¹⁹ Live bacteria contained in probiotics are acceptable for human consumption and are able to have a beneficial effect on the health of the body when consumed in adequate amounts.²⁰

Among the probiotic *strains* that has now been developed as a commercial product for oral health care include, namely *Weisella cibaria* Chonnam Medical University or *Weisella cibaria* CMU.^{6,12,21} Nonetheless, information on the effectiveness including safety aspects on general body health and effects on psychosocial health from the use of *Weisella cibaria* CMU as an oral probiotic for halitosis therapy from clinical research in humans is still limited. The purpose of this scoping review is to analyze the effectiveness of using *Weisella cibaria* CMU as an oral probiotic for halitosis therapy from various human clinical research results so that it can be useful as a basis for consideration in choosing alternative halitosis therapies that are proven to be safer and more effective, especially through the use of oral probiotics so as to increase the success of halitosis therapy in general.

METHOD

In accordance with the Preferred Reporting Item Guidelines for Methods of Systematic Review and Meta Analysis (PRISMA), the flow of article selection for this review was represented by a diagram.²² The analysis criteria include PICO (Population, Intervention, Comparison, Outcome). Three electronic databases were used to search for scientific articles, namely PubMed, Google Scholar and ResearchGate from January 2013-June 2023. The Boolean search used in the search process for scientific articles to be studied include "halitosis" AND "oral probiotics" AND "Weissella cibaria CMU." Figure 1 shows the process of filtering articles according to the inclusion and exclusion criteria to acquire papers for this review's analysis.

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RESULTS

A total of 88 scientific articles relevant to the Boolean search “halitosis” AND “oral probiotics” AND “*Weissella cibaria* CMU” were obtained in this review with details identified from the PubMed data base with 4 articles, Google Scholar with 80 articles, and ResearchGate with 4 articles. The screening articles from these data bases after removing duplicated articles and abstract only, 80 articles. Screening based on exclusion criteria by reading the title and abstract, 56 articles were obtained. Eligibility of articles after reading the entire contents of the article based on the exclusion criteria, 4 articles were obtained. The selection of articles to

be included in the final qualitative synthesis of this review was based on the inclusion criteria, with a total of 4 articles. All studies analyzed in this review were conducted in Korea with double-blind, randomized, placebo-controlled study with the total number of halitosis-affected people (according to the inclusion criteria of each researcher) who received oral probiotic intervention *Weissella cibaria* CMU were 142 people, while the control subjects who received placebo totaled to 137 people. A summary of all articles that meet the eligibility for final synthesis related to the effectiveness of using *Weissella cibaria* CMU as an oral probiotic for halitosis therapy, can be seen in Table 1

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Table 1

No	Authors-Year	Subjects	Amount of Subjects	Design of Study	Intervention	Results
1	Lee DS et al (2020)	Students in Kongwon National University of Korea; 20-39 years of age; Meet the inclusion criteria	Healthy adult with halitosis whose exhibit VSC level >1.5ng/10ml (n=34)	Randomized Double Blind Placebo	Probiotic group was given an 800 mg tablet (to let it melt and suck on the tongue) contained 1.0x10 ⁸ CFU/g of probiotic <i>W. cibaria</i> CMU (oracCMU; Orapharm, Inc, Seoul, Korea) taken once daily every night before bed time after brushing their teeth for 8 weeks; Control group was a placebo tablet from the same manufacturer without probiotic <i>W. cibaria</i> CMU	Mean OLT scores and concentration of VSC revealed lower significant (P<0.05) in probiotic groups at week 4; Mean BBI scores were lower significant (P<0.05) in the probiotic groups at week 8; Level of <i>W. cibaria</i> in the probiotic group was higher significant (P<0.05) than in control group from baseline to 8 weeks; Vital sign, hematological finding and blood chemistry were within normal ranges in both group
2	Lee DS et al (2021)	College students in Gangwon province, South Korea; Over 20 years of age; Meet the inclusion criteria	Healthy adult with halitosis whose exhibit VSC level >1.5ng/10ml (n=34); Healthy control (n=28)	Randomized Double Blind Placebo	Probiotic group was given an 800 mg tablet (to let it dissolved on the tongue) that contain 1.0x10 ⁸ CFU/g of probiotic <i>W. cibaria</i> CMU (oracCMU; Orapharm, Inc, Seoul, Korea) taken one tablet once daily every night before bed time after brushing their teeth for 8 weeks; Control group was a placebo tablet without probiotic <i>W. cibaria</i> CMU	Subjective halitosis if they have perceived they had no halitosis after treatment were significant higher in probiotic group than control (p<0.030); Depression (p=0.605) and self esteem (p=0.688) before and after treatment which no significant difference between the two group; Oral health status related quality of life before and after treatment getting better significant in test group than control (p=0.036); No severity of symptoms were identified as adverse event towards the participants safety.
3	Kim DH et al (2020)	Adults men and women with 20-halitosis whose 70years of age; exhibit VSC level >0.15ng/ml and who score >2 points in a halitosis sensory evaluation test (n=29); Healthy control (n=29)	Healthy adult with halitosis whose exhibit VSC level >1.5ng/10ml (n=34) Control Trial	Randomized Double Blind Placebo	Probiotic group was given the powder form contained 1.0x10 ⁸ CFU/bag of probiotic <i>W. cibaria</i> CMU (Oradentics, Co.,ltd, Seoul, Korea) placed in the mouth immediately before going to bed and left until the powder got melted for 8 weeks; Control group was administered malodextrin alone as a filler in powder production without <i>W. cibaria</i> CMU	Mean concentration of VSC was reduced by 0.030 ng/ml in the probiotic group and increased by 0.005 ng/ml in the control group after week 8 of ingestion but not statistically significant. Score self evaluation of improvement was halitosis reduction significant after week 4 (P<0.030) and week 8 (P=0.038) of ingestion in the probiotic group compared to the control group.
4	Han HS et al (2023)	Participants from the Department of Periodontology, Seoul National University Dental Hospital were aged 20-70years; Meet the inclusion criteria	Healthy adult with halitosis whose exhibit VSC level >1.5ng/10ml (n=45) Control Trial	Randomized Double Blind Placebo	Probiotic group was given an 800 mg tablet (to chew and suck) contained 1.0x10 ⁸ CFU/g of probiotic <i>W. cibaria</i> CMU (oracCMU; Orapharm, Inc, Seoul, Korea) taken once tablet every night before bed time after brushing their teeth for 8 weeks; Control group was a placebo tablet from the same manufacturer without probiotic <i>W. cibaria</i> CMU	Total VSC was significantly lower in probiotic group compared to control group at baseline and at 8 weeks; BBI score probiotic group was significant different compare than control group at week 8 which probiotic group showed a decreased and control group showed an increased (p=0.008); Levels of <i>W. cibaria</i> were significant higher in the probiotics group than in the control group (p<0.001) at week 8; Psychosocial health involved depression (p=0.019), oral health related quality of life (p=0.001) and objective oral health status (p=0.007) significantly improved from baseline to week 8 in probiotic group; No clinical significant changes in indicator vital signs, hematological finding, blood chemistry result of safety evaluation in the probiotic group

DISCUSSION

An oral probiotic method is currently being developed as an alternative halitosis therapy, because it can inhibit the growth of pathogenic bacteria without causing adverse effects on the normal microflora ecosystem in the oral cavity.¹² One of the oral probiotics that has been developed as a commercial product for oral health care, especially for halitosis therapy, is the *Weissella cibaria* CMU (Chonnam Medical University)

strain of bacteria.^{3,5,12} Saliva of the children in Korea, ages 4 to 7, with good oral health, were used as subjects for the isolation of this probiotic species of *Weissella cibaria* CMU.¹² *Weissella cibaria* species is a group of lactic acid bacteria with round morphology (*coccus*) or *rod*, is classified as a type of facultative anaerobic gram-positive bacteria from the family *Leuconostocaceae*, order *Lactobacillales*, class *Bacilli*, and phylum *Firmicutes*.²³ The ability of *W. cibaria*

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CMU as a probiotic to reduce halitosis has been proven from various human clinical studies analyzed in this review.^{3,5,12,18} The intervention in the treatment group of all studies analyzed in this review was the administration of probiotic *W.cibaria* CMU tablets (containing 1×10^8 CFU/gr) which were sucked and allowed to dissolve in the oral cavity with a frequency of administration 1 x every night before bedtime for a period of 8 weeks, except in the Kim DH et al study in 2020 which provided probiotic *W.cibaria* CMU preparations in powder form (containing 1.0×10^8 CFU/bag) and allowed them dissolve in the oral cavity.^{3,5,12,18} The control group of all the studies mentioned above, received placebo tablets without any probiotic content, except for the Kim DH et al study in 2020 which provided placebos in the form of maltodextrin without probiotic content of *W.cibaria* CMU.^{3,5,12,18}

The improvement in halitosis conditions in the treatment group (probiotics) from the results of the studies analyzed in this review, appears to occur due to a significant increase in the number of *W.cibaria* CMU bacteria after the administration of probiotic *W.cibaria* CMU tablet preparations to the treatment group at week 8 as shown from the results of Lee DS et al in 2020 and Han HS et al in 2023, so that it might take the place of the bacteria's colony in the oral cavity that causes halitosis which in turn has an impact on reducing the concentration of VSC in the oral cavity.^{3,12} The VSCs that contribute to the onset of halitosis are known to composed of the following components, namely hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulfide (CH_3SCH_3), which are produced by gram negative anaerobic bacteria in the oral cavity, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia* and *Treponema denticola* through protein degradation (L-cysteine, L-methionine that contain sulfur).^{10,12} Study conducted by Jang HJ et al, which proves the ability of VSC inhibition (especially H_2S and CH_3SH) produced by *Fusobacterium nucleatum* bacteria by *W.cibaria* CMU as an oral probiotic at 97% and the ability of VSC inhibition (especially H_2S and CH_3SH) produced by *Porphyromonas gingivalis* bacteria at 93.9%.²⁴

The mechanism underlying the ability of probiotic *Weissella cibaria* CMU to improve halitosis conditions in this review, according to Kang MS et al in 2005 cited by Lee DS et al in 2020, can occur through competition for the attachment of probiotic *W.cibaria* CMU to epithelial cells of the oral cavity.¹² Another mechanism based on Jang HJ et al research, has proven that probiotic *W.cibaria* CMU has the greatest coaggregate ability at 81.2% against pathogenic bacteria *Fusobacterium nucleatum* that produce VSC when compared to other types of lactic acid bacteria such as *Lactobacillus salivarius*, *Streptococcus salivarius*, and *Lactobacillus reuteri*.²⁴ *Weissella cibaria* *Weissella cibaria* CMU bacteria functioning as an oral probiotic to reduce halitosis can also occur through the mechanism of production of antibacterial ingredients, namely hydrogen peroxide, which is proven to be

produced in larger quantities by *Weissella cibaria* CMU probiotics when compared to other types of lactic acid bacteria such as *Lactobacillus salivarius*, *Streptococcus salivarius* dan *Lactobacillus reuteri*.²⁴ The antibacterial ability of *Weissella cibaria* CMU as an oral probiotic in inhibiting the growth of pathogenic bacteria *Fusobacterium nucleatum* and *Porphyromonas gingivalis* was shown to reach more than 95%.²⁴ Anti-bacterial ingredients in the form of hydrogen peroxide produced by *Weissella cibaria* CMU as an oral probiotic are further known to produce hydroxyl radicals that play a role in inducing changes in the oral bacterial community and inhibiting the growth of pathogenic bacteria, including *Fusobacterium nucleatum* bacteria that produce VSC.²⁴ Furthermore, according to Thomas EL cited by Jang HJ et al,²⁴ hydroxyl radical action of hydrogen peroxide is known to be able to react with nucleic acids that causes damage to pathogenic bacterial genes, as well as increase permeability and denature proteins in pathogenic bacterial cells that produce VSC as the cause of halitosis.

The decrease in VSC levels and the amount of oral probiotic *Weissella cibaria* CMU after administration of probiotic tablet or powder preparations containing *Weissella cibaria* CMU from various research results mentioned above, Furthermore, it can affect the assessment of the *Bad Breath Improvement* (BBI) score in the probiotic group which is proven to be significantly lower than the control group at week 8 from the results of the study of Lee DS et al in 2020 and seems to be in line with the results of the study of Han HS et al in 2023.^{3,12} The research from Kim DH et al in 2020 has also proven a significant reduction in the self-evaluation of improvement score at weeks 4 and 8 in the probiotic group compared to the control group.⁵ Furthermore, research by Lee DS et al in 2021, has proven that the halitosis subjectivity assessment score, which means that the subject feels that they do not have halitosis, appears to be significantly higher in the probiotic group compared to the control group.¹²

Assessment of oral health status related to quality of life before and after the intervention, appeared to have significantly improved in the probiotic group compared to the control group from the results of the study by Lee DS et al in 2021.¹⁸ Psychosocial health status including depression, oral health related to quality of life and oral health status has shown to have significantly improved from the baseline period to week 8 in the probiotic group compared to the control group from the results of the study by Han HS et al in 2023.³ Assessment of depression and self-confidence levels before and after intervention from the results of Lee DS et al research in 2021 on the contrary showed results that were not significantly different between the probiotic group and the control group.¹⁸ The level of self-confidence in participants in Lee DS et al study in 2021 was further explained that it was not only influenced by halitosis, but could also be influenced by various other factors such as satisfaction in interpersonal relationships.¹⁸ Regarding the safety aspect, the

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use of *W.cibaria* CMU as an oral probiotic for halitosis sufferers from the results of Lee DS et al 2020 study, was proven to be safe because it showed a range of normal values based on the examination of body vital signs, hematological findings and blood chemistry, for both the probiotic group and the control group. The same results have also been shown from the results of Lee DS et al in 2021 and Han HS et al in 2023.^{3,18} The results of research that are also quite interesting to be observed in this review, namely the research by Kim DH et al in 2020, have shown that the decrease in VSC concentration that occurred in the *Weissella cibaria* CMU probiotic group in powder dosage form, proved to have no significant difference when compared to the control group.⁵ Related to this, Kim HJ et al in 2019 has explained that the use of probiotic *W.cibaria* CMU in the form of commercial tablet preparations is more recommended than capsule and powder preparations because tablet preparations are designed for slow dissolution of probiotic preparations in the mouth so as to extend the duration and period of probiotic activity in the mouth.²⁵

CONCLUSION

Clinical studies indicate that consuming *Weissella cibaria* CMU bacteria as an oral probiotic is safe for the body and effective in improving halitosis because it significantly reduces VSC levels, has a positive impact on the balance of oral microflora, increases halitosis assessment improvement scores, and enhances oral health in connection with quality of life, so it can be considered as an alternative to support halitosis therapy

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