ALTAMASH JOURNAL OF DENTISTRY AND MEDICINE

REVIEW ARTICLE

The Impact of Vaping on the Oral Microbiome: A Comprehensive Review of Bacterial Effects

Afsheen Maqsood¹, Daud Mirza¹, Seema Ashraf², Sarwat Jahan³

1. Bahria University Dental College, Karachi, Pakistan

2. Technical Advisor and Public Analyst, Sindh Food Authority, Karachi, Pakistan

3. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Karachi university, Pakistan

ABSTRACT

Recent research investigating into the impact of vaping on the oral microbiome reveals significant consequences for oral health. The scientific literature highlights that vaping induces notable changes in the composition of oral bacteria. This alteration favors the proliferation of pathogenic bacteria associated with gingival disease while concurrently diminishing the concentration of beneficial bacteria crucial for maintaining oral health. The resultant disruption in the delicate balance of the oral microbiome creates a conducive environment for the development of various oral health problems. Among these consequences are an increased risk of dental caries, increased susceptibility to periodontitis, and an elevated likelihood of developing oral lesions and cancer. Understanding the complicated mechanisms through which vaping exerts these effects on oral bacteria is imperative. Such insights can inform the development of targeted and effective strategies aimed at promoting oral health and, critically, preventing vaping-related oral diseases. As the prevalence of vaping continues to rise, prioritizing research in this area becomes paramount for preserving an overall oral wellbeing.

AJDM

Keywords: Oral bacteria, Vaping, Smoking, Oral Health, Caries, Periodontitis

This is an Open Access article distributed under the terms of the creative common Attribution-Noncommercial 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provide the original work is properly cited.

Corresponding Author

Dr. Afsheen Maqsood Bahria University Dental College, Karachi, Pakistan Afsheenmaqsood.bumdc@bahria.edu.pk

INTRODUCTION

Vaping refers to the inhalation of vaporized substances typically generated by electronic cigarettes (e-cigarettes) or similar devices. These devices heat a liquid, often containing nicotine, flavorings, and other chemicals, to produce an aerosol that is inhaled.¹ The rise in the popularity of vaping can be attributed to several factors. One key factor is the perception that vaping is a potentially less harmful alternative to traditional cigarette smoking. Many people see vaping as a way to satisfy nicotine cravings without exposure to the harmful tar and combustion byproducts associated with conventional tobacco smoking.² Additionally, the appeal of various flavored e-liquids has contributed to the widespread adoption of vaping, particularly among younger demographics. The availability of a wide range of flavors, along with the perception of vaping as a trendy and socially acceptable activity, has attracted a significant number of users.³ Marketing strategies, ease of accessibility, and the convenience of vaping devices have also played roles in the popularity of vaping. The development of sleek, portable devices and the perception of vaping as a modern and technologically advanced practice have further contributed to its rise in popularity in recent years.⁴

Oral health and the intricate ecosystem of the oral microbiome are fundamentally significant for overall wellbeing, considering the pivotal role the mouth plays as the gateway to the body. Within the oral cavity, a diverse community of microorganisms, including bacteria, viruses, and fungi, forms the oral microbiome, impacting various aspects of health.⁵ Digestively, the oral cavity initiates the breakdown of food through mastication and saliva, underscoring the importance of a balanced microbiome for proper digestion and nutrient absorption. Furthermore, the oral microbiome supports the immune system, acting as a frontline defense against harmful pathogens.⁶ Dental health is closely intertwined with the oral microbiome, as imbalances can lead to issues such as cavities and periodontal disease.⁷ Research also suggests connections between oral health and systemic conditions, emphasizing the far-reaching implications of the oral microbiome on cardiovascular, metabolic, and respiratory health. Additionally, maintaining a healthy oral microbiome is crucial for preventing respiratory infections, as oral bacteria can potentially be aspirated into the lungs.⁸ Beyond the physiological aspects, oral health influences psychosocial

well-being, impacting an individual's confidence and social interactions. In essence, prioritizing oral health and nurturing a balanced oral microbiome contribute not only to dental well-being but also to a comprehensive approach to overall health and disease prevention.⁹ Regular dental hygiene practices, a balanced diet, and measures to preserve the oral microbiome integrity collectively raise a holistic approach to oral and systemic well-being.¹⁰ The purpose of this review is to thoroughly investigate and analyze the impact of vaping on oral cavity bacteria. The review aimed to explore the potential changes, disruptions, or alterations in the oral microbiome associated with the practice of vaping. By examining existing literature and research findings, the review seeks to provide a comprehensive understanding of how vaping may influence the composition and dynamics of oral bacteria. This investigation is crucial for assessing the potential oral health implications of vaping and contributing valuable insights to the broader understanding of the consequences of electronic cigarette use on the microbial environment within the oral cavity.

MATERIALS AND METHODS

The search strategy employed to identify pertinent research articles on the effects of vaping on oral cavity bacteria involved a systematic and comprehensive approach. A set of relevant keywords and phrases were chosen to capture the essential components of the research focus. This included terms such as "vaping," "e-cigarettes," "oral microbiome," "oral bacteria," and related variations. Databases known for hosting academic and scientific literature, such as PubMed, Scopus, and Web of Science, were selected as primary sources for article retrieval. Boolean operators (AND, OR) were used to combine and refine search terms, ensuring that the results were both specific and comprehensive. For instance, the search query may have included combinations like "vaping AND oral microbiome" or "e-cigarettes OR oral bacteria." Criteria were established to include only peer-reviewed articles, reviews, and original studies directly relevant to the effects of vaping on oral cavity bacteria. Non-English language articles and those not meeting specific quality standards were excluded. Depending on the research focus and recent developments in the field, a time frame 2013 - 2023) for publication was set to ensure the inclusion of the most current and relevant research. In addition to electronic

databases, specific journals known for publishing relevant content were hand-searched to identify additional articles that might not have been captured through the electronic search alone. Citation tracking was employed to identify additional articles by examining the references of relevant papers. This helped ensure a comprehensive review of the existing literature. Two reviewers (AM) and (SA) were part of the screening and selection process in this review. The comprehensive search strategy resulted in the identification of 26 articles, reflecting a thorough examination of the existing literature.

Inclusion Criteria

Articles had to directly address the impact of vaping on oral cavity bacteria, including studies focusing on changes in the oral microbiome associated with electronic cigarette use. Only peer-reviewed articles from reputable academic journals were included to ensure the reliability and validity of the research. Articles within a specified timeframe were considered, typically within the last decade, to include the most recent and relevant studies reflecting current knowledge on the subject. Various study designs were considered, including experimental studies, observational studies, clinical trials, and systematic reviews, to provide a comprehensive overview of the research landscape. Studies involving human participants were prioritized, as they are directly relevant to the potential impact of vaping on the oral microbiome in a real-world context. **Exclusion Criteria**

Articles not published in English were excluded due to potential language barriers and limitations in the ability to assess and interpret the content accurately. Studies conducted solely on animals were excluded to maintain a focus on the direct implications of vaping on the human oral microbiome. Articles that did not specifically address the relationship between vaping and oral cavity bacteria were excluded to maintain the precision and relevance of the review. Non-peer-reviewed sources, such as conference abstracts, opinion pieces, and editorials, were excluded to ensure the reliability and rigor of the included studies. Studies lacking sufficient data or clarity regarding their methodologies, results, or conclusions were excluded to uphold the quality standards of the review. The review incorporates a diverse range of studies to comprehensively explore the effects of vaping on oral cavity bacteria. Controlled experiments designed to investigate the direct impact of vaping on the oral microbiome. These studies may involve exposure to ecigarette aerosols in laboratory settings, allowing for controlled observations and measurements. Research that observes and analyzes patterns, correlations, and changes in the oral microbiome among individuals who engage in vaping. This includes cross-sectional studies, cohort studies, and case-control studies. Interventions or experiments conducted in clinical settings to assess the effects of vaping on oral health, specifically focusing on changes in the composition of oral bacteria. Comprehensive reviews that synthesize and analyze findings from multiple studies to provide a consolidated overview of the cumulative evidence regarding the impact of vaping on the oral microbiome. Studies involving human participants, ensuring that the research directly addresses the implications of vaping on the oral microbiome in a relevant and real-world context.

Effects of vaping on oral bacteria

Research exploring the changes in bacterial composition caused by vaping has revealed significant insights into the impact of electronic cigarette use on the oral microbiome. Several studies have indicated that vaping can lead to alterations in the oral microbiome, with shifts in the abundance and diversity of bacterial species.¹¹ Notably, an increase in the prevalence of potentially harmful bacteria, such as Streptococcus mutans, has been observed, linking vaping to a potential risk for dental caries and other oral health issues. Moreover, the aerosols produced by e-cigarettes may create an environment conducive to dysbiosis, disrupting the balance of the oral microbiome and contributing to inflammation in the oral cavity.¹² Nicotine, a common component in e-cigarettes, has also been implicated in influencing the growth and adherence of specific bacteria, potentially playing a role in microbial community shifts. Importantly, individual variability has been emphasized, with factors like vaping frequency, duration, and the composition of e-cigarette aerosols contributing to differences in microbial responses among users.¹³

Research comparing the abundance of beneficial and harmful bacteria in vapers and non-vapers reveals intriguing patterns within the oral microbiome. In individuals who vape, there is evidence suggesting a potential reduction in the abundance of beneficial bacteria, possibly influenced by the components present in e-cigarette aerosols.¹⁴ Simultaneously, vapers may experience an increase in harmful bacteria, such as Streptococcus mutans, which is associated with an elevated risk of dental caries. This shift in microbial composition could indicate an unfavorable oral environment for individuals who engage in electronic

cigarette use.¹⁵ Conversely, non-vapers appear to maintain a more balanced and diverse population of beneficial bacteria in their oral microbiome. Traditional oral hygiene practices, without exposure to e-cigarette aerosols, contribute to a potentially healthier microbial landscape in non-vapers. The overall microbial diversity in nonvapers remains more stable, with a more favorable balance between beneficial and harmful bacterial species. However, individual responses may vary, and ongoing research is necessary to uncover the full extent of the impact of vaping on the oral microbiome and its implications for oral health.¹ The observed alterations in the oral microbiome associated with vaping can be attributed to several potential mechanisms stemming from the complex interplay between electronic cigarette aerosols and the intricate microbial community in the oral cavity. The chemical constituents present in e-cigarette aerosols, such as nicotine, flavorings, and additives, likely play a direct role in influencing the growth, adherence, and viability of oral bacteria. Notably, nicotine has been scrutinized for its potential impact on bacterial adhesion and biofilm formation, contributing to shifts in microbial composition.¹⁷ Vaping-induced inflammation in the oral cavity creates an environment conducive to dysbiosis, where inflammatory responses alter the ecological niche and influence the survival of specific bacterial species. Additionally, impaired immune responses associated with vaping may further disrupt the balance between beneficial and harmful bacteria in the oral microbiome.¹⁸ The heat generated during vaping, along with direct exposure to vaporized substances, may selectively favor the growth of certain bacterial species while inhibiting others.

Furthermore, changes in salivary flow and pH levels linked





to vaping can influence the conditions for bacterial proliferation.¹⁹

DISCUSSION

Vaping's impact on oral bacteria can be explained through several potential mechanisms, each contributing to the complex interplay between electronic cigarette aerosols and the delicate oral ecosystem. Direct toxicity emerges as a significant factor, given that vaping aerosol encompasses a cocktail of chemicals, including propylene glycol, glycerin, nicotine, and flavorings. These components, known to exert various effects on biological systems, can directly harm oral bacteria, disrupting their growth and balance within the oral microbiome. Furthermore, the indirect effects of vaping play a crucial role in altering the oral environment.²⁰ Vaping has been associated with the induction of inflammation in the oral cavity, creating conditions conducive to the proliferation of harmful bacteria. This inflammatory response may disturb the equilibrium of the oral microbiome, potentially favoring the growth of pathogenic species.²¹ Another noteworthy mechanism is the potential reduction in salivary flow associated with vaping. Saliva plays a pivotal role in maintaining oral health by rinsing away debris and harmful microorganisms. The decrease in salivary flow caused by vaping may compromise this natural defense mechanism, allowing harmful bacteria to persist and potentially contribute to oral health issues.²² The altered oral microbiome induced by vaping heightens the risk of various dental and gum diseases through intricate mechanisms that disrupt the delicate balance of oral microbial communities. Vaping has been associated with an increase in harmful bacteria, particularly Streptococcus mutans, intensifying the risk of dental caries by contributing to enamel demineralization. Furthermore, the altered microbiome facilitates the formation of bacterial biofilms and plaque on dental surfaces, fostering an environment conducive to gingivitis and periodontitis.²³ Chronic inflammation triggered by vaping can compromise the integrity of gum tissues, leading to symptoms characteristic of gum diseases, such as bleeding and swelling. Dysbiosis resulting from vaping disrupts the equilibrium between beneficial and harmful bacteria, weakening the natural defense mechanisms that maintain oral health. Impaired immune responses further exacerbate susceptibility to bacterial infections, while changes in salivary flow and

pH create an environment favoring acidogenic bacteria, promoting enamel erosion and the development of dental caries. Collectively, these interconnected factors underscore the multifaceted impact of vaping on the oral microbiome, emphasizing the heightened risk of dental and gum diseases associated with electronic cigarette use.^{24,25} The potential link between vaping and oral cancer is a matter of increasing concern, prompting ongoing research to understand the implications of electronic cigarette use on oral health. Electronic cigarette aerosols, containing nicotine and various chemicals, undergo complex reactions during vaping that may produce harmful compounds. While nicotine itself is not classified as a carcinogen, its influence on cellular processes, such as cell proliferation and angiogenesis, raises concerns about its potential contribution to cancer risk. Vaping has been associated with increased inflammation and oxidative stress in the oral cavity, known factors in the development of cancer. Moreover, alterations in the oral microbiome due to vaping may create an environment conducive to inflammation and dysbiosis, which are implicated in cancer progression.^{25,26} Limited long-term studies and the relatively recent emergence of vaping as a phenomenon underscore the need for continued research to elucidate the relationship between vaping and oral cancer. As our understanding evolves, it becomes increasingly important to address potential health risks associated with electronic cigarette use and formulate informed public health recommendations.

Oral health care providers play a pivotal role in safeguarding the well-being of their patients, and the emerging evidence on the potential risks associated with vaping underscores the importance of proactive screening and education. Given the impact of vaping on the oral microbiome, increased inflammation, and potential links to oral cancer, oral health care professionals are uniquely positioned to identify and address the oral health consequences of electronic cigarette use. By routinely screening patients for vaping habits, providers can gather crucial information about potential risk factors and tailor their preventive and treatment strategies accordingly. Moreover, educating patients about the risks of vaping and its potential impact on oral health empowers them to make informed decisions about their well-being. Dental professionals can offer guidance on smoking cessation programs, oral hygiene practices, and the maintenance of a healthy oral microbiome. This proactive approach not only contributes to the prevention of oral health issues associated with vaping but also fosters a collaborative and informed patient-provider relationship, ultimately promoting comprehensive oral health and overall wellbeing.²⁶⁻²⁸

The limitations of the reviewed studies on the effects of vaping on oral health include the predominantly shortterm nature of the research, hindering a comprehensive understanding of the potential long-term consequences. Heterogeneity in vaping products, variations in e-liquid compositions, and diverse user behaviors introduce challenges in generalizing findings across studies. The deficient number of randomized controlled trials (RCTs) limits the ability to establish definitive causal relationships between vaping and specific oral health outcomes. These limitations highlight the necessity for future research to overcome these challenges and provide a more nuanced and conclusive understanding of the impact of vaping on oral health.

Healthcare providers should integrate routine screening for vaping habits into patient assessments, ensuring comprehensive discussions about the potential risks to oral health. Including vaping history in patient records can aid in personalized treatment planning and risk assessment. Proposing smoking cessation counseling and support programs for patients who vape, in collaboration with interdisciplinary healthcare teams, is crucial. Public health officials should develop targeted awareness campaigns on the risks of vaping for oral health, employing various media channels for broad dissemination. Integrating vaping awareness and oral health education into school curricula can discourage initiation among adolescents. Advocating for evidence-based policies and regulations that address the marketing, sale, and accessibility of vaping products, particularly to minors, is essential. Researchers should conduct long-term, prospective studies to assess the sustained impact of vaping on oral health and mechanistic research to elucidate pathways through which vaping influences the oral cavity. Large-scale populationbased studies can evaluate vaping prevalence, patterns, and associations with oral health outcomes across diverse demographics. Mitigating negative effects requires community-based interventions, integration of vaping cessation components into existing tobacco programs, regulatory measures limiting availability, and collaboration with educational institutions for comprehensive prevention and cessation initiatives. This multifaceted approach aims

to minimize potential harm and promote informed decisionmaking among individuals using electronic cigarettes.

CONCLUSION

The review on the effects of vaping on oral health has highlighted several key findings. Vaping has been associated with alterations in the oral microbiome, an increase in harmful bacteria like Streptococcus mutans, and increased inflammation in the oral cavity. These changes create an environment conducive to dental problems, including cavities and gingival diseases. Moreover, potential links between vaping and oral cancer have raised significant concerns, although comprehensive evidence is still evolving. The potential dangers of vaping for oral health are highlighted by the disruption of the delicate balance in the oral microbiome, the inflammatory response, and the uncertain long-term consequences of exposure to e-cigarette aerosols. Given the limited current understanding and the dynamic nature of the vaping landscape, further research is imperative to clarify the mechanisms and long-term effects. Public health interventions should focus on raising awareness among oral health care providers to screen for vaping habits, educate patients about associated risks, and contribute to smoking cessation programs. The multifaceted impact of vaping on oral health necessitates a comprehensive and collaborative approach to minimize potential harm and promote well-informed decision-making among individuals using electronic cigarettes.

Author contributions

AM, SA, SJ, DM: literature review, developed the design and methodology, writing of the manuscript, comprehended the study, performed revisions, supervision. DM, AM, SA: Conceived the idea of the study, performed revisions, and writing of the manuscript, Funding acquisition.

Funding

No funding.

Institution ethical board approval Not applicable.

Acknowledgement:

The authors would like to express their sincere gratitude to all the researchers and scholars whose work laid the foundation for this review. We extend our appreciation to the participants of the studies included in our analysis, without whom this review would not have been possible. Special thanks to the reviewers whose insightful feedback significantly enhanced the quality of this review article. Lastly, we acknowledge the broader scientific community for their contributions to the field of oral health, as it has greatly enriched our understanding of the complex relationship between vaping and oral health.

Conflict of interest

No conflict of interest.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). (2023, August 31). Vaping.

https://www.cdc.gov/tobacco/basic_information/ecigarettes/index.htm

2. National Academies of Sciences, Engineering, and Medicine. (2018, January). Public health consequences of e-cigarettes. National

https://nap.nationalacademies.org/catalog/24952/public-health-consequences-of-e-cigarettes.

3. Eissenberg T. Now is the time for effective regulation regarding tobacco smoking using a water pipe (Hookah). Journal of Adolescent Health. 2019; 64(6):685-6. 4. Lyu JC, Huang P, Jiang N, Ling PM. A systematic review of e-cigarette marketing communication: messages, communication channels, and strategies. International Journal of Environmental Research and Public Health. 2022;19(15):9263.

5. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486(7402):207-14.

6. Bengmark S. Gut microbiota, immune development and function. Pharmacological research. 2013; 69(1):87-113.

7. Sedghi L, DiMassa V, Harrington A, Lynch SV, Kapila YL. The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontology 2000. 2021; 87(1):107-31.
8. Martínez-García M, Hernández-Lemus E. Periodontal inflammation and systemic diseases: an overview. Frontiers in physiology. 2021; 12:709438.

9. Nishizawa T. A Possible Association Between Oral Bacteria and Aspiration Pneumonia: Do Oral Bacteria Have Roles in the Pathogenesis of Aspiration Pneumonia?.

Aspiration Pneumonia: The Current Clinical Giant for Respiratory Physicians. 2020:97-104.

10. Spanemberg JC, Cardoso JA, Slob EM, López-López J. Quality of life related to oral health and its impact in adults. Journal of stomatology, oral and maxillofacial surgery. 2019; 120(3):234-9.

11. Martínez-García M, Hernández-Lemus E. Periodontal inflammation and systemic diseases: an overview. Frontiers in physiology. 2021; 12(3):709438.

12. Chopyk J, Bojanowski CM, Shin J, Moshensky A, Fuentes AL, Bonde SS, Chuki D, Pride DT, Crotty Alexander LE. Compositional differences in the oral microbiome of e-cigarette users. Frontiers in Microbiology. 2021; 12(2):599664.

13. Catala-Valentin A, Bernard JN, Caldwell M, Maxson J, Moore SD, Andl CD. E-cigarette aerosol exposure favors the growth and colonization of oral Streptococcus mutans compared to commensal Streptococci. Microbiology spectrum. 2022 Apr 27; 10(2):e02421-21.

14. Yang I, Rodriguez J, Young Wright C, Hu YJ. Oral microbiome of electronic cigarette users: A cross?sectional exploration. Oral Diseases. 2023; 29(4):1875-84. 15. Zhang Y, Wang X, Li H, Ni C, Du Z, Yan F. Human oral microbiota and its modulation for oral health. Biomedicine & Pharmacotherapy. 2018; 99(2):883-93. 16. Wagenknecht DR, BalHaddad AA, Gregory RL. Effects of nicotine on oral microorganisms, human tissues, and the interactions between them. Current Oral Health Reports. 2018;5(1):78-87.

17. Mousa WK, Chehadeh F, Husband S. Recent advances in understanding the structure and function of the human microbiome. Frontiers in Microbiology. 2022; 13:825338. 18. Thomas SC, Xu F, Pushalkar S, Lin Z, Thakor N, Vardhan M, Flaminio Z, Khodadadi-Jamayran A, Vasconcelos R, Akapo A, Queiroz E. Electronic cigarette use promotes a unique periodontal microbiome. Mbio. 2022; 13(1):e00075-22.

Szumilas P, Wilk A, Szumilas K, Karakiewicz B. The effects of e-cigarette aerosol on oral cavity cells and tissues: a narrative review. Toxics. 2022; 10(2):74.
 Ganesan SM, Dabdoub SM, Nagaraja HN, Scott ML,

Pamulapati S, Berman ML, Shields PG, Wewers ME, Kumar PS. Adverse effects of electronic cigarettes on the disease-naive oral microbiome. Science advances. 2020 May; 6(22):eaaz0108.

21. Stewart CJ, Auchtung TA, Ajami NJ, Velasquez K, Smith DP, De La Garza II R, Salas R, Petrosino JF. Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study. PeerJ. 2018 Apr 30; 6:e4693.

22. Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, Jörres RA, Fromme H. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. International journal of hygiene and environmental health. 2014; 217(6):628-37.

23. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, Stone MD, Khoddam R, Samet JM, Audrain-McGovern J. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. Jama. 2015; 314(7):700-7.

24. Begum SF, Nagajothi G, Latha KS, Sandeep G, Sreekanth B, Kumar CS, Rajendra W, Maddu N. Possible role of nicotine and cotinine on nitroxidative stress and antioxidant content in saliva of smokeless tobacco consumers. Practical laboratory medicine. 2018; 12:e00105. 25. Gfroerer J, Dube SR, King BA, Garrett BE, Babb S, McAfee T. Vital signs: current cigarette smoking among adults aged? 18 years with mental illness-United States, 2009-2011. Morbidity and Mortality Weekly Report. 2013; 62(5):81.

26. He H, Pan Z, Wu J, Hu C, Bai L, Lyu J. Health effects of tobacco at the global, regional, and national levels: results from the 2019 global burden of disease study. Nicotine and Tobacco Research. 2022;24(6):864-70. 27. Holliday R, Chaffee BW, Jakubovics NS, Kist R, Preshaw PM. Electronic cigarettes and oral health. Journal of dental research. 2021 Aug;100(9):906-13. 28. Clark LN, Mian TK. Adverse Effects of Electronic Cigarettes on the Disease-Naïve Oral Microbiome. Internal Medicine Alert. 2022;44(2).