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THE INFLUENCE OF THE INTESTINAL MICROBIOTA ON CARDIOVASCULAR HEALTH: AN INTEGRATIVE REVIEW

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Abstract: Introduction: The gut microbiota plays a key role in human health, influencing various physiological processes in cardiovascular health. Objective: To analyze the scientific research that investigates the relationship between the intestinal microbiota and cardiovascular health, in particular the existing evidence on how the composition of the intestinal microbiota affects the development of cardiovascular diseases. Methodology: Articles relevant to the work were selected, including clinical trial, meta-analysis, literature review and systematic literature review, through the platform's data base PubMed, using the keywords "Gut microbiota" and "Heart disease". Results: The studies investigated different aspects of the relationship between intestinal microbiota and cardiovascular health, including the influence of intestinal dysbiosis, microbial diversity, metabolites produced by the microbiota and the immunological mechanisms involved. The results suggest that alterations in the composition of the intestinal microbiota may be associated with an increased risk of cardiovascular diseases, including atherosclerosis, hypertension and ischemic heart disease. Conclusion: Based on the integrative literature review, there is growing evidence that the gut microbiota plays a relevant role in cardiovascular health. Understanding the mechanisms involved in this relationship can provide important insights for the development of new therapeutic strategies and interventions based on the modulation of the intestinal microbiota. However, further studies are needed to fully elucidate the underlying mechanisms and establish effective interventions to improve cardiovascular health through manipulation of the gut microbiota.
Keywords: Gut microbiota. Cardiovascular diseases. Cardiovascular Health.

INTRODUCTION

Human health is profoundly impacted by the gut microbiota, which plays an essential role in influencing a wide range of physiological processes, including those related to cardiovascular health. Recent studies have investigated the relationship between the intestinal microbiota and cardiovascular health, revealing significant opportunities and challenges in this area of research (CHEN et al., 2021; KAZEMIAN et al., 2021; WITKOWSKI et al., 2020). These investigations have provided insights into the role and mechanism by which the gut microbiota is involved in cardiovascular disease, paving the way for new therapeutic approaches and preventive interventions (CHEN et al., 2021; KAZEMIAN et al., 2021; WITKOWSKI et al, 2020).

This complex relationship involves mechanisms that include the production of metabolites by the intestinal microbiota, which can affect lipid metabolism, inflammation and endothelial function (CHEN et al., 2021; WITKOWSKI et al., 2020). In addition, the intestinal microbiota plays a key role in modulating the immune system and regulating blood pressure, crucial factors for cardiovascular health (KAZEMIAN et al., 2021; WITKOWSKI et al., 2020).

Accumulation of trimethylamine N-oxide (TMAO) has been linked to pathological processes that contribute to heart failure, such as inflammation, endothelial dysfunction, oxidative stress, and cardiac remodeling. Additionally, TMAO has been linked to cardiovascular risk factors such as atherosclerosis, hypertension, and cardiovascular disease in general. These findings raised concerns about the potential of TMAO as a predictive and therapeutic biomarker in cardiovascular disease (ZHANG et al., 2020).

Despite the growing interest in the relationship between gut microbiota and cardiovascular health, there are still challenges to be overcome. The heterogeneity of the studies and the need for additional research are important points to be considered (CHEN et al., 2021; KAZEMIAN et al., 2021). Furthermore, the identification of specific biomarkers and the development of therapeutic strategies based on the modulation of the intestinal microbiota are evolving areas (WITKOWSKI et al., 2020). Advances in these fields can provide a better understanding of the mechanisms involved in the relationship between the intestinal microbiota and cardiovascular health, as well as the development of personalized therapies and effective preventive interventions (WITKOWSKI et al., 2020).

METHODOLOGY

The present study employed a research methodology based on qualitative analysis, through an integrative literature review, with the aim of establishing connections between data from previous studies, examining valid questions and reviewing theories on the subject in question.

The searches were carried out using the MEDLINE editor (PubMed), with the search terms "Gut microbiota" and "Heart disease". Articles in English published in the last 5 years (2018 to 2023) were selected, with full text available, with the following methodologies: clinical trial, meta-analysis, bibliographic review or systematic literature review, focusing on the relationship between the intestinal microbiota and health cardiovascular. Studies that did not belong to these methodologies were excluded.

After carrying out the careful analysis of the integrative review, the relevant data were organized in a table containing information such as author's name, year of publication, article title and conclusion. Initially, 73

searches were identified in PubMed. After applying the established inclusion and exclusion criteria, a total of 8 articles were selected to compose the integrative review. The compilation of this table was performed using the Excel 2016 software. These selected articles served as a basis to support the discussion of the main results found in the context of the relationship between the intestinal microbiota and cardiovascular health.

RESULTS

FIGURE 1 presents the flowchart exposing the criteria for choosing scientific articles to compose the integrative review. Initially, 73 articles were found according to the methodlogy. Posteriorly, titles and abstracts were observed, and 14 articles were chosen for comprehensive reading. In summary,8 articles were selected for discussion and composition of the integrative review.

Thus, TABLE 1 presents a comparative discussion subdivided into author and year, title of work and conclusion in each research.

DISCUSSION

The study by Han Xu, et al (2023) presents a systematic review to address the relationship between the intestinal microbiota and myocardial fibrosis. The intestinal microbiota plays a fundamental role in the homeostasis of the immune system and in the regulation of the inflammatory response. In addition, the gut microbiota is involved in the production of metabolites that can influence inflammation and cardiac tissue remodeling. The presence of intestinal microbiota dysbiosis, characterized by changes in the composition and function of intestinal bacteria, has been associated with the development and progression of myocardial fibrosis. Based on the study, changing the composition of the gut microbiota can affect cardiac inflammation, oxidative stress, immune response and cardiac tissue remodeling. Furthermore, preclinical studies have shown that probiotic administration can reduce cardiac inflammation and improve cardiac function in animal models of myocardial fibrosis.

Qiujin Jia, et al (2018), emphasized the crucial importance of the intestinal microbiota in the regulation of energy metabolism, redox balance, systemic inflammation and hormonal homeostasis, with this influence being responsible for the production of metabolites, modulation of the immune system and activation of inflammatory pathways. Such effects can lead to changes in hormone levels, lipid metabolism and systemic inflammatory response, contributing to the development of cardiovascular diseases. Furthermore, the western diet, characterized by being rich in saturated fats and sugars, is associated with changes in the composition of the intestinal microbiota and a higher risk of cardiovascular diseases. On the other hand, diets rich in fiber and fermented foods promote the diversity and balance of the intestinal microbiota, conferring cardiovascular benefits. In agreement with Han xu, et al (2023), the authors correlate the use of probiotics, prebiotics and fecal microbiota transplantation with an improvement in cardiovascular health in preclinical and clinical studies.

The study conducted by Yang, et al (2019), highlights the importance of Trimethylamine oxide (TMAO) as a biomarker dependent on the intestinal microbiota, associated with the progression of cardiovascular diseases, when found at high levels, and evaluates the mechanisms involved in the relationship between TMAO, inflammation, clinical prognosis and its potential as a therapeutic target. TMAO stimulates the activation of inflammatory cells, such as monocytes and macrophages, leading to the production of pro-inflammatory cytokines and an increase in the systemic inflammatory response. This

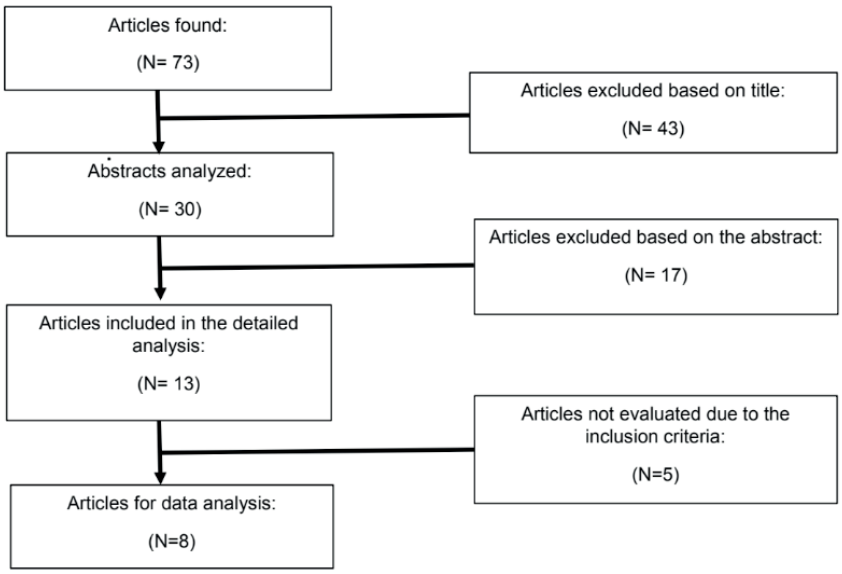

FIGURE 1: flowchart with the criteria used for inclusion and exclusion of scientific articles

Source: Sady et al (2023)

Author and Year	Study Title	Conclusions
Shengjie Yang et al. (2019)	Gut Microbiota-Dependent Marker TMAO in Promoting Cardiovascular Disease	The production of trimethylamine N-oxide (TMAO) by the intestinal microbiota is associated with the development of cardiovascular diseases. TMAO can promote inflammation, endothelial dysfunction and atherosclerotic plaque formation. This finding suggests that TMAO may serve as a potential therapeutic target for cardiovascular disease.
Qiujin Jia et al. (2019)	Endocrine organs of cardiovascular diseases: Gut microbiota	The study highlights the influence of gut microbiota on endocrine homeostasis, including the production of peptides and hormones that affect cardiovascular health. Bidirectional communication between the gut and the heart via the microbiota may play an important role in regulating metabolism and the cardiovascular system.
Esther Forkosh and Yaron Ilan (2019)	The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy	The study highlights the importance of heart-gut communication via the heart-gut axis, including the influence of gut microbiota on cardiovascular function and the pathogenesis of atherosclerosis and congestive heart failure. The heart-gut axis is a potential new target for cardiovascular disease therapies.
Huagang Liu et al. (2020)	The Role of the Gut Microbiota in Coronary Heart Disease	The gut microbiota predisposes a key point in the pathogenesis of coronary artery disease. Intestinal dysbiosis can lead to chronic low-grade inflammation, dysregulation of lipid metabolism, and activation of the immune system, all of which contribute to the development of coronary artery disease.

Myungsuk Kim et al. (2020)	Sequence meets function -microbiota and cardiovascular disease	The study highlights the relationship between gut microbiota and cardiovascular disease, including the microbiota's role in modulating lipid metabolism, inflammation, endothelial function, and energy homeostasis, all of which play a role in the pathogenesis of cardiovascular disease.
Estefania Sanchez-Rodriguez et al. (2020)	The Gut Microbiota and Its Implication in the Development of Atherosclerosis and Related Cardiovascular Diseases	Intestinal dysbiosis is associated with the development of atherosclerosis and related cardiovascular diseases. The intestinal microbiota affects lipid metabolism, inflammation, endothelial function and the immune response, playing a crucial role in the development and progression of cardiovascular diseases.
Jing Lu et al. (2022)	Immune mechanism of gut microbiota and its metabolites in the occurrence and development of cardiovascular diseases	The study explores the role of gut microbiota metabolites in the occurrence and development of cardiovascular disease, highlighting the interaction between microbial metabolites, the immune system and inflammation. Immune regulation mediated by the intestinal microbiota is of paramount importance in the control of cardiovascular diseases.
Han Xu et al. (2023)	Gut microbiota and myocardial fibrosis	Gut microbiota plays a critical role in the progression of myocardial fibrosis. Interactions between intestinal microorganisms and the host can influence inflammation and the immune response, contributing to the development of myocardial fibrosis and, potentially, cardiovascular disease.

TABLE 1: studies included in the process on the relationship of intestinal microbiota in cardiovascular health

Source: Sady et al (2023)

chronic inflammatory state contributes to the progression of atherosclerosis, endothelial dysfunction and cardiac remodeling, resulting in cardiovascular complications. The authors also explore the possibility of targeting TMAO as a potential therapeutic target. Strategies to reduce TMAO levels include dietary modification, use of selective antibiotics to suppress TMAO production by the gut microbiota, and development of drugs that inhibit TMAO formation or its detrimental effects on the body.

Liu, et al (2020) discuss the mechanisms by which the gut microbiota may contribute to coronary heart disease. These mechanisms include the production of metabolites derived from dietary compounds, such as trimethylamine N-oxide (TMAO) and bile acids, which may promote inflammation, endothelial dysfunction, and production of vasoactive compounds, as a consequence, predisposing to problems such as dyslipidemia and hypertension. In addition, the microbiota can modulate the immune response, affecting the activity of immune cells involved in atherosclerosis, such as macrophages and T cells. According to the authors, dysbiosis may contribute to increased insulin resistance and increased inflammation contributing to the activation of immune system cells. This may favor the development and progression of coronary heart disease, and as a consequence of increased insulin resistance, the onset of diabetes mellitus. In addition, the intestinal microbiota also plays a role in the metabolization of phenolic compounds present in foods, such as polyphenols, which have antioxidant and anti-inflammatory properties that may protect against coronary heart disease. In conclusion, the authors link the production of short-chain fatty acids (SCFAs), such as butyrate, and some anti-inflammatory properties, and these may exert beneficial effects on cardiovascular health; reduced production of SCFAs due to changes in the gut microbiota may be associated with an increased risk of coronary heart disease.

Sanchez-Rodriguez, et al (2020) conducted a narrative review to evaluate the relationship between the gut microbiota and the development of atherosclerosis and related cardiovascular diseases. The relationship of the gut microbiota and gut permeability was discussed, where bacterial toxins and endotoxins present in the microbiota, can cross the gut barrier and enter the bloodstream, triggering a systemic inflammatory response and contributing to the development of atherosclerosis. In addition, the role of lipopolysaccharides (LPS), which are Gram-negative bacterial cell wall components released into the intestinal lumen, and their direct relationship in increasing systemic inflammation and possible development of atherosclerosis was addressed. The authors also evaluate the gut microbiota and its role in converting primary bile acids to secondary bile acids, and may affect the ratio of primary and secondary bile acids, which has implications for lipid metabolism, inflammation, and the development of atherosclerosis. As a solution, microbiota modulation strategies, such as the use of probiotics and prebiotics, show potential to modulate cardiovascular risk. In addition, fecal transplantation, which involves the transfer of healthy microbiota from a donor to a recipient, has been investigated as a possible therapy to reduce inflammation and improve cardiovascular health.

Kim, et al (2021), evaluated the metabolism of L-carnitine and TMAO and their association with the intestinal microbiota, through a literature review. The conversion of L-carnitine to trimethylamine (TMA) is followed by oxidation of TMA in the liver, forming trimethylamine oxide (TMAO), with elevated levels of TMAO being associated with an increased risk of atherosclerosis and

cardiovascular events. Certain species of intestinal bacteria, such as those belonging to the genus Prevotella and Enterobacteriaceae, are associated with increased production of TMAO. Another aspect was the approach to the relationship between intestinal dysbiosis and systemic inflammation, with increased levels of inflammatory markers in the blood, such as C-reactive protein (CRP) and pro-inflammatory cytokines responsible for chronic low-grade inflammation, predisposing the progression of atherosclerosis and the development of adverse cardiovascular events. In line with Liu, et al (2020), the authors correlate the production of short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, by the intestinal microbiota, as a cardiovascular protection pathway, reducing inflammation, improving lipid metabolism and regulating vascular function.

The study carried out by Forkosh and Ilan (2019) emphasizes the relationship of the intestinal microbiota as a pathogenesis of congestive heart failure (CHF), through intestinal dysbiosis, which induces the increased production of toxic metabolites, such as secondary bile acids, causing adverse effects on the heart and worsening congestive heart failure. In this context, intestinal dysbiosis is associated with increased intestinal permeability, which allows the translocation of bacterial toxins into the bloodstream, triggering a systemic inflammatory response that promotes the formation of plaque in the arteries. In addition, they highlight the importance in the pathogenesis of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which can be released from the intestinal microbiota, triggering a cascade of inflammatory events in the heart. In agreement with Sanchez-Rodriguez, et al (2020), the authors include the use of probiotics and prebiotics to restore the balance of the microbiota, as well as the development of targeted therapies, such as selective antibiotics or modulators of the heart-gut axis to control the cardiovascular disorders.

Analogous to the conclusions of Yang, et al (2019); Liu, et al (2020) and Kim, et al (2021), the authors Jing Lu, et al (2022), highlight that the intestinal microbiota plays a fundamental role in the regulation of the immune system and, consequently, generates protection for cardiovascular health, as it interacts in a complex way with cells of the immune system and produces a variety of metabolites that can affect the inflammatory response, these metabolites being microbial products, such as short-chain fatty acids (SCFA) and microbial peptides. As an example, the authors mention the role of SCFA derived from bacterial fermentation and their association with a decrease in the inflammatory response and protection against the development of atherosclerosis. On the other hand, the authors state that trimethylamine N-oxide (TMAO) can also influence platelet function and blood clotting, increasing the risk of thrombotic events, generating a worse cardiovascular prognosis, suggesting its role as a prognostic biomarker. With regard to microbial peptides, the authors report their interaction with cells of the immune system, such as lymphocytes, macrophages and dendritic cells, triggering specific immune responses, which may act as signals to regulate the activation, differentiation and function of these cells, influencing the inflammatory and immune response. On the other hand, microbial peptides can also modulate intestinal permeability, endothelial response and the production of inflammatory cytokines, having an impact on the occurrence and development of cardiovascular diseases.

CONCLUSION

The interaction between the intestinal microbiota and the cardiovascular system is

increasingly recognized, highlighting the role of the heart-gut axis. The communication between these two systems through the intestinal microbiota influences the organism's homeostasis, including the regulation of metabolism, inflammation and immune response, key factors in the development of cardiovascular diseases.

Based on the analysis of the included articles, it is concluded that alterations in the composition and function of the intestinal microbiota have been associated with endocrine disorders related to cardiovascular diseases, such as atherosclerosis, heart failure and arterial hypertension. These alterations can affect lipid metabolism, energy balance, blood pressure regulation and the inflammatory response, contributing to the development of these conditions.

The presence of the TMAO marker, which is produced by the intestinal microbiota through the metabolism of certain nutrients, has been associated with an increased risk of cardiovascular disease. TMAO has the ability to promote inflammation in endothelial cells, which can lead to vascular dysfunction, atherosclerotic plaque formation and increased risk of adverse cardiovascular events.

Another relevant aspect is the influence of the intestinal microbiota on the metabolism of bioactive compounds, such as short-chain fatty acids. These fatty acids have anti-inflammatory properties and may have beneficial effects on cardiovascular health, helping to reduce blood pressure and improve endothelial function.

Although there are still gaps in knowledge and aspects to be clarified, the reviewed studies point to the possibility of using therapeutic strategies based on the modulation of the intestinal microbiota to prevent and treat cardiovascular diseases. The use of probiotics, prebiotics and specific diets can help promote microbiota balance and improve cardiovascular health.

In conclusion, the analyzed studies highlight the importance of the intestinal microbiota in the pathophysiology of cardiovascular diseases and provide promising insights for the development of innovative therapeutic approaches. Understanding the mechanisms involved in this complex interaction may pave the way for targeted therapeutic interventions aimed at reducing the burden of cardiovascular disease and improving the cardiovascular health of the population.

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