International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn23231

Major roles of the gut microbiota and microRNAs in cardiovascular disease events: a systematic review

Vanessa Piovesan Freitas Assumpção[1*], Otavio Queiroz Assumpção[1]

[1] Costa Rica Hospital Foundation- Vitale Clinic, Costa Rica, MS, Brazil.

*Corresponding Author: Dra. Vanessa Piovesan Freitas Assumpção. Costa Rica Hospital Foundation- Vitale Clinic, Costa Rica, MS, Brazil.
E-mail: vanessapiovesanfreitas@hotmail.com
DOI: https://doi.org/10.54448/ijn23231
Received: 04-16-2023; Revised: 06-20-2023; Accepted: 06-29-2023; Published: 07-03-2023; IJN-id: e23231

Abstract

Introduction: Gut microbiota (GM) is an essential mediator in the health of GM and has been identified as the origin of several diseases by influencing cell signaling and T cell receptor pathways in the central nervous system. Several microRNAs participate in signaling networks through GM intervention. The interaction between GM and miRNAs plays a crucial role in vascular dysfunction. GM can metabolize L-carnitine, choline, and phosphatidylcholine and produce vascular-toxic metabolites such as trimethylamine-Noxide (TMAO), which is associated with the atherosclerotic process. Nutrology and dietary therapy represent important strategies, especially with the use of plant-derived miRNAs to modify GM. **Objective:** To carry out a systematic review to highlight the main roles of the gut microbiota and microRNAs in cardiovascular disease events. **Methods:** The present study followed a concise systematic review model (PRISMA). The literary search process was carried out from March to May 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022. The low quality of evidence was attributed to reports of cases, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** The total of 126 studies were found for eligibility analysis, and then 42 of the 64 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2 =88.7%>50%. It was concluded that the gut microbiota can be influenced by diet, genetics, and environmental factors. Changes in the microbial population can lead to multiple diseases, including cardiovascular disease. miRNAs have been known as important regulators of several biological functions, and are also involved in the pathogenesis of cardiovascular diseases. There is evidence that disturbances in the gut microbiota and derived metabolites impair the development of atherosclerotic cardiovascular disease. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis.

Keywords: Gut microbiota. Cardiovascular diseases. microRNAs. Nutrology.

Introduction

Gut microbiota (GM) is an essential mediator in health and disease, relating to various organs and systems of the body, including the brain, lungs, liver, bones, cardiovascular system, and others. As an example, GM-derived metabolites such as shortchain fatty acid butyrate (SCFA) bind GM and modulate physiology. Furthermore, GM has been identified as the origin of several diseases by influencing related cell signaling pathways such as the WNT/beta-catenin pathway in colorectal cancer and T cell receptor signaling in the central nervous system. Furthermore, several microRNAs participate in signaling networks through GM intervention. The interaction between GM and microRNAs (miRNAs) plays a crucial role in vascular dysfunction and hepatocellular carcinoma **[1,2]**.

Furthermore, GM composition is influenced by host genetics and environmental factors. Recent studies have

shown that GM is not just a passive participant in our health, but can also actively regulate our functions through genes, proteins, and metabolites **[3-6]**. Dysbiosis can lead to various diseases, not only gastrointestinal but also disorders of the lung, brain, heart, and immune system **[7-9]**. Dysbiosis plays an important role in cardiovascular diseases (CVD), mainly by activating a pro-inflammatory state in the body and favoring the atherosclerotic process **[10,11]**.

In this context, GM can metabolize L-carnitine, choline, and phosphatidylcholine and produce vascular-toxic metabolites, such as trimethylamine-N-oxide (TMAO), which is associated with the atherosclerotic process **[12]**. A continuous inflammatory state in the gut can facilitate the transit of bacteria and their metabolites into the bloodstream, thus maintaining chronic inflammation and favoring the development of atherosclerotic plaques, increasing the risk of coronary heart disease, stroke, and other acute complications **[11,13]**.

In this sense, miRNAs are regulators in the processes of gene expression in the host and are linked to specific bacteria **[14]**. They enter bacterial cells by endocytosis, influencing the GM by stimulating or inhibiting the expansion of certain bacterial species **[15-17]**. In the miRNAs-gut microbiota connection, miRNAs have effects on intestinal cell proliferation and differentiation, gut architecture, and barrier function **[18]**. Some studies have shown that GM can have an impact on miRNAs, modulating gene expression in the host **[14,19]**.

In this scenario, the association between circulating miRNAs and CVD has been widely investigated to discover new possible diagnostic markers **[20-23]**. The miRNAsgut microbiota relationship is especially involved in the regulation of epithelial dysfunction **[9]**. GM can influence RNA genes affiliated with miRNA classes, such as vascular miR-204, miR-10B, or miR-181, decreasing or increasing the risk of developing atherosclerosis **[24-27]**.

Still in this aspect, nutrology and dietary therapy represent important strategies, especially with the use of plant-derived miRNAs to modify GM **[28,29]**. For example, studies in mice have shown that ginger-derived exosomes contain miRNAs that can influence GM by increasing fatty acid metabolism. Wang et al. observed an increase in Bifidobacterium species and SCFA-producing bacteria, reducing body weight, hepatic steatosis, low-grade inflammation, and insulin resistance **[29,30]**. Probiotics can restore GM balance to the benefit of the host **[31]**. The role of miRNAs in GM modulation highlighted their possible implication in the molecular mechanism of action of probiotics **[15,16]**.

Therefore, this study aimed to carry out a systematic review to highlight the main functions of the gut microbiota and microRNAs in cardiovascular disease events.

Methods

Study Design

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and metaanalysis-HTTP: //www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from March to May 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022, using the descriptors (MeSH Terms): *Gut microbiota. Cardiovascular diseases. microRNAs. Nutrology*, and using the Booleans "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

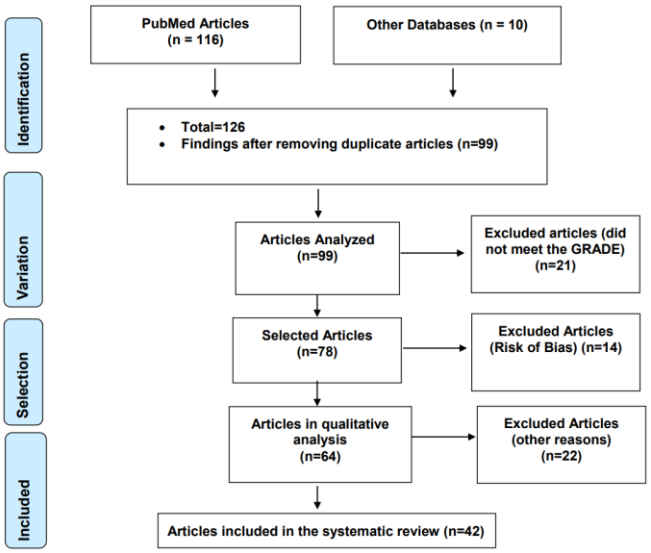
Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Cohen test (d)).

Literary Review Results

Summary of Findings

It was found 126 studies that underwent eligibility analysis, and then 42 of the 64 total studies were selected for the present systematic review (**Figure 1**), considering in the first instance the level of scientific evidence of studies in study types such as metaanalysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2 =88.7% >50%.

Figure 1. Flowchart showing the article selection process.



Major Clinical Outcomes

GM can be influenced by diet, genetics, and environmental factors. Any change in its composition results in pathophysiological changes that can further influence the evolution of several conditions, including CVD. MicroRNAs interact with GM to modulate host gene expression. Circulating microRNAs are stable against degradation due to their closure in extracellular vesicles **[32]**.

Many studies have highlighted the connection between miRNAs and GM, especially in the case of dysbiosis, which leads to intestinal epithelial barrier dysfunction and inflammatory response **[30-32]**. MicroRNAs are particularly involved in the regulation of intestinal epithelial cells (IEC) **[28-30]**. Some studies have shown that fecal miRNAs can influence GM composition. miR-375 plays an important role in the production of the mucus layer in epithelial cells and influences stem cell proliferation in the intestinal epithelium. The suppression of miR-381-3p allows nuclear receptor-related protein-mediated IEC proliferation while gut barrier function is being enhanced **[1,2]**.

Furthermore, GM can produce biologically active metabolites, which can further influence the physiological processes of the host. Changes in the microbial population can lead to multiple diseases, including CVD **[22]**. Dysbiosis, intestinal inflammation, and altered intestinal barrier can result in high concentrations of bacterial structural elements and microbial metabolites in the circulation, including trimethylamine N-oxide (TMAO) and short-chain fatty acids, which can further favor the evolution of CVD. Low concentrations of microbes that produce butyrate have been associated with heart failure and coronary artery disease **[11]**.

In addition, phenylacetylglutamine has the potential to favor negative cardiovascular phenotypes in hosts, by acting on adrenergic receptors. TMAO is a metabolite often found in Western diets, rich in lecithin, choline, phosphatidylcholine, and carnitine, which predicted cardiovascular risk in some clinical studies and amplified the atherosclerotic process in animal models **[33-35]**.

Besides, miRNAs have been known as important regulators of several biological functions, being also involved in the pathogenesis of CVD **[33,34]**. The most abundant miRNAs in cardiac tissue are miR-1, let-7, miR-133, miR-126-3p, miR-30c, and miR26a **[35]**, while in arteries the most frequent miRNAs are miR-145, let -7, miR-125b, miR-125a, miR-23 and miR-143 **[36-38]**.

In this scenario, there is evidence of disturbances in GM and derived metabolites that impair the development of atherosclerotic cardiovascular disease (ASCVD). One study analyzed 30 patients for the relationship of GM to coronary artery disease (CAD) and 30 age- and sex-matched healthy controls to identify microbial metabolites associated with CAD, which were then evaluated in an independent population of ASCVD patients and controls (n=256). Indole-3-propionic acid (IPA), a tryptophan metabolite exclusively derived from microorganisms, was the most down-regulated metabolite in patients with CAD. Circulating IPA was then shown in an independent population to be associated with ASCVD risk. In murine- and human-derived macrophages, IPA administration promoted cholesterol efflux from macrophages to ApoA-I through an undescribed miR-1425p/ABCA1 signaling pathway. Furthermore, the miR-142-5p/ABCA1/reverse cholesterol transport axis in macrophages was dysregulated in CAD patients and correlated with changes in circulating IPA levels **[39]**.

Also, a Mediterranean diet style has been reported to be associated with a lower degree of inflammation biomarkers and a protective role in cardiovascular and cerebrovascular events. We report a new positive association between baseline plasma ceramide concentrations and cardiovascular events and how adherence to a Mediterranean-style diet may influence the potential negative relationship between elevated plasma ceramide concentrations and CVD. Several randomized clinical trials have shown the positive effects of the Mediterranean diet style on various cardiovascular risk factors such as body mass index, waist circumference, blood lipids, blood pressure, inflammatory markers and adhesion molecules, and

diabetes and how these advantages of Mediterranean diets are maintained compared to a low-fat diet. The PREDIMED study showed that the incidence of cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra virgin olive oil or nuts than among those assigned to a low-fat diet **[40]**.

In this context, oxidative stress and inflammation interact in the development of diabetic atherosclerosis. Intracellular hyperglycemia promotes the production of mitochondrial reactive oxygen species (ROS), increased formation of intracellular advanced glycation end products, activation of protein kinase C, and increased polyol pathway flux. ROS directly increases the expression of inflammatory and adhesion factors, the formation of oxidized low-density lipoprotein, and insulin resistance, as well as activates the ubiquitin pathway, inhibits the activation of AMP-protein kinase and adiponectin, decreases the activity of endothelial nitric oxide synthase, all accelerating atherosclerosis. Changes in GM composition and changes in microRNA expression that influence the regulation of target genes that occur in diabetes interact with increased ROS and inflammation to promote atherosclerosis **[41]**.

In this sense, finally, it is understood that atherosclerosis is characterized by the accumulation of lipids and chronic inflammation. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis. YsRNA-5p transcripts promote foam cell apoptosis and inflammatory responses by binding to Ro60 in vitro and in vivo. YRNAs can regulate the progression of atherosclerosis by binding to several proteins, including nucleolin, Ro60, La, hnRNPK, hnRNPI, YBX1, and ELAVL1. YRNAs can be derived from miRNAs and piRNAs; in particular, Y4sRNA-3p and Y5sRNA-3p in humans are also called piR-hsa-32167 and piR-hsa-116589, respectively. Furthermore, YRNAs are detectable in blood plasma and YRNA ratios are potential biomarkers for inflammatory diseases, including atherosclerosis. YsRNAs are released by apoptotic macrophages in the blood of patients with coronary artery disease and are potential biomarkers of foam cell apoptosis to monitor the pathogenesis of atherosclerosis. Circulating YsRNAs are also present in platelets. Furthermore, GM also expresses YRNAs and YsRNAs **[42]**.

Conclusion

It was concluded that the gut microbiota can be influenced by diet, genetics, and environmental factors. Changes in the microbial population can lead to multiple diseases, including cardiovascular disease. microRNAs have been known as important regulators of several biological functions, and are also involved in the pathogenesis of cardiovascular diseases. There is evidence that disturbances in the gut microbiota and derived metabolites impair the development of atherosclerotic cardiovascular disease. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis.

Acknowledgement

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

References

1. Feng Q, Chen WD, Wang YD. Gut Microbiota: An Integral Moderator in Health and Disease. Front Microbiol. 2018 Feb 21;9:151. doi: 10.3389/fmicb.2018.00151.
2. Mody D, Verma V, Rani V. Modulating host gene expression via gut microbiomemicroRNA interplay to treat human diseases. Crit Rev Microbiol. 2021 Sep;47(5):596-611. doi: 10.1080/1040841X.2021.1907739.
3. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017, 13:e1006654. 10.1371/journal.ppat.1006654.
4. Shukla SD, Budden KF, Neal R, Hansbro PM.

Microbiome effects on immunity, health and disease in the lung. Clin Transl Immunology. 2017, 6:e133. 10.1038/cti.2017.6.

5. Van de Wiele T, Van Praet JT, Marzorati M, Drennan MB, Elewaut D. How the microbiota shapes rheumatic diseases. Nat Rev Rheumatol. 2016, 12:398–411. 10.1038/nrrheum.2016.85.
6. Lynch JB, Hsiao EY. Microbiomes as sources of emergent host phenotypes. Science. 2019, 365:1405–9. 10.1126/science.aay0240.
7. Chang CS, Kao CY. Current understanding of the gut microbiota shaping mechanisms. J Biomed Sci. 2019, 26:59. 10.1186/s12929-019-0554-5.
8. Qin Y, Wade PA. Crosstalk between the microbiome and epigenome: messages from bugs. J Biochem. 2018, 163:105–12. 10.1093/jb/mvx080.
9. Li M, Chen WD, Wang YD. The roles of the gut microbiota-miRNA interaction in the host pathophysiology. Mol Med. 2020 26:101. 10.1186/s10020-020-00234-7.
10. Ionescu RF, Boroghina SC, Cretoiu SM. Is there a link between the gut microbiome and arterial hypertension? J Hypertens Res. 2021, 7:12–7. Available online at: http://www.hypertens.org/images/202103/jhr-202103070103.pdf [Google Scholar].
11. Cretoiu D, Ionescu RF, Enache RM, Cretoiu SM, Voinea SC. Gut microbiome, functional food, atherosclerosis, and vascular calcifications-is there a missing link? Microorganisms. 2021, 9:1913. 10.3390/microorganisms9091913.
12. Ding L, Chang M, Guo Y, Zhang L, Xue C, Yanagita T, et al.. TrimethylamineN-oxide (TMAO)-induced atherosclerosis is associated with bile acid metabolism. Lipids Health Dis. 2018, 17:286. 10.1186/s12944-018-0939-6.
13. Komaroff AL. The microbiome and risk for atherosclerosis. JAMA. 2018, 319:2381. 10.1001/jama.2018.5240.
14. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ. 2019, 7:e7502. 10.7717/peerj.7502.
15. Behrouzi A, Ashrafian F, Mazaheri H, Lari A, Nouri M, Rad FR, et al.. The importance of interaction between MicroRNAs and gut microbiota in several pathways. Microb Pathog. 2020, 144:104200. 10.1016/j.micpath.2020.104200.
16. Spinler JK, Karri V, Hirschi KD. Planting the microbiome. Trends Microbiol. 2019, 27:90–3. 10.1016/j.tim.2018.12.001.
17. Zhao L, Zhou X, Cai W, Shi R, Yang G, Yuan L. Host intestinal epithelium derived MIRNAS shape the microbiota and its implication in cardiovascular diseases. J Am Coll Cardiol. 2017, 69:1075. 10.1016/S0735-1097(17)34464-9.
18. Ding S, Liu G, Jiang H, Fang J. MicroRNA determines the fate of intestinal epithelial cell differentiation and regulates intestinal diseases. Curr Protein Pept Sci. 2019, 20:666–73. 10.2174/1389203720666190125110626.
19. Watson AJM, Hall LJ. Regulation of host gene expression by gut microbiota. Gastroenterology. 2013, 144:841–4. 10.1053/j.gastro.2013.02.028.
20. Sarshar M, Scribano D, Ambrosi C, Palamara AT, Masotti A. Fecal microRNAs as innovative biomarkers of intestinal diseases and effective players in hostmicrobiome interactions. Cancers. 2020, 12:2174. 10.3390/cancers12082174.
21. Gaspar BS, Ionescu RF, Enache RM, Dobrica EC, Cretoiu SM, Cretoiu D, et al.. Extracellular Vesicles as Intercellular Communication Vehicles in Regenerative Medicine. Available online at: https://www.intechopen.com/onlinefirst/79775 (accessed april 10, 2023).
22. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al.. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 2008, 18:997–1006. 10.1038/cr.2008.282.
23. Creemers EE, Tijsen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? Circ Res. 2012, 110:483–95. 10.1161/CIRCRESAHA.111.247452.
24. Genecards.org (2022). Available online at: https://www.genecards.org/cgibin/carddisp.pl?gene=MIR10B (accessed march 16, 2023).
25. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004, 109:III27–32. 10.1161/01.CIR.0000131515.03336.f8.
26. Wang D, Xia M, Yan X, Li D, Wang L, Xu Y, et al.. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. Circ Res. 2012, 111:967–81. 10.1161/CIRCRESAHA.112.266502.
27. Bodogai M, O'Connell J, Kim K, Kim Y, Moritoh K, Chen C, et al.. Commensal bacteria contribute to insulin resistance in aging by activating innate B1a cells. Sci Transl Med. 2018, 10:eaat4271. 10.1126/scitranslmed.aat4271.
28. Zhao Y, Zeng Y, Zeng D, Wang H, Zhou M, Sun N, et al.. Probiotics and microRNA: their roles in the host-microbe interactions. Front Microbiol.

2020, 11:604462. 10.3389/fmicb.2020.604462.

29. Nagai M, Obata Y, Takahashi D, Hase K. Fine-tuning of the mucosal barrier and metabolic systems using the diet-microbial metabolite axis. Int Immunopharmacol. 2016, 37:79–86. 10.1016/j.intimp.2016.04.001.
30. Wang J, Wang P, Li D, Hu X, Chen F. Beneficial effects of ginger on prevention of obesity through modulation of gut microbiota in mice. Eur J Nutr. 2020, 59:699–718. 10.1007/s00394-019-01938-1.
31. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al.. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic: expert consensus document. Nat Rev Gastroenterol Hepatol. 2014, 11:506–14. 10.1038/nrgastro.2014.66.
32. Ionescu RF, Enache RM, Cretoiu SM, Cretoiu D. The Interplay Between Gut Microbiota and miRNAs in Cardiovascular Diseases. Front Cardiovasc Med. 2022 Mar 16;9:856901. doi: 10.3389/fcvm.2022.856901.
33. Romaine SPR, Tomaszewski M, Condorelli G, Samani NJ. MicroRNAs in cardiovascular disease: an introduction for clinicians. Heart. 2015, 101:921–8. 10.1136/heartjnl-2013-305402.
34. Ionescu RF, Cretoiu SM. MicroRNAs as monitoring markers for right-sided heart failure and congestive hepatopathy. J Med Life. 2021, 14:142–7. 10.25122/jml2021-0071.
35. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. Curr Biol. 2002, 12:735–9. 10.1016/S0960-9822(02)00809-6.
36. Ji R, Cheng Y, Yue J, Yang J, Liu X, Chen H, et al.. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of microRNA in vascular neointimal lesion formation. Circ Res. 2007, 100:1579–88. 10.1161/CIRCRESAHA.106.141986.
37. Luo X, Zhang H, Xiao J, Wang Z. Regulation of human cardiac ion channel genes by microRNAs: theoretical perspective and pathophysiological implications. Cell Physiol Biochem. 2010, 25:571–86. 10.1159/000315076.
38. Wang Z, Lu Y, Yang B. MicroRNAs and atrial fibrillation: new fundamentals. Cardiovasc Res. 2011, 89:710–21. 10.1093/cvr/cvq350.
39. Xue H, Chen X, Yu C, Deng Y, Zhang Y, Chen S, Chen X, Chen K, Yang Y, Ling W. Gut Microbially Produced Indole-3-Propionic Acid Inhibits Atherosclerosis by Promoting Reverse Cholesterol Transport and Its Deficiency Is Causally Related to Atherosclerotic Cardiovascular Disease. Circ Res. 2022 Aug 19;131(5):404-420. doi: 10.1161/CIRCRESAHA.122.321253.
40. Tuttolomondo A, Simonetta I, Daidone M, Mogavero A, Ortello A, Pinto A. Metabolic and Vascular Effect of the Mediterranean Diet. Int J Mol Sci. 2019 Sep 23;20(19):4716. doi: 10.3390/ijms20194716.
41. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W, Xie X. New insights into oxidative stress and inflammation during diabetes mellitusaccelerated atherosclerosis. Redox Biol. 2019 Jan;20:247-260. doi: 10.1016/j.redox.2018.09.025.
42. Chen W, Li L, Wang J, Li Q, Zhang R, Wang S, Wu Y, Xing D. Extracellular vesicle YRNA in atherosclerosis. Clin Chim Acta. 2021 Jun;517:15-22. doi: 10.1016/j.cca.2021.02.003.