

REVIEW ARTICLE

Endothelial Dysfunction in Diabetic Nephropathy: A Vascular Perspective on Renal Protection

Divagar Arivalagan¹, Shivkumar Patel², Mohamad Nur Firdaus^{3,*}, Praveena Vijaya Devan⁴¹ Cantonment Board General Hospital, Acharya Tulsi Rd, Pallavaram, Chennai-600044, Tamil Nadu, India² SBKS Medical Institute and Research Center, Vadodara, Gujarat 391760, India³ Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia⁴ University of Cyberjaya, Persiaran Bestari, Cyber 11, 63000 Cyberjaya, Selangor, Malaysia***Corresponding Author:** Mohamad Nur FirdausFaculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Email: u2002168@siswa.um.edu.my**Article info****Received:** 17 June 2024**Accepted:** 2 August 2024**Keywords:** Diabetic nephropathy, Renal injury, Endothelial Biomarkers**How to cite this article:** Divagar Arivalagan, Shivkumar Patel, Mohamad Nur Firdaus, Praveena Vijaya Devan. (2024). A network pharmacology approach for investigating the multi-target mechanisms of Betanin in the treatment of Colon cancer (CC), 1(3), 27-31 Retrieved from <http://archmedrep.com/index.php/amr/article/view/21>

Abstract

Diabetic nephropathy (DN), a leading cause of end-stage renal disease worldwide, is increasingly recognized as a disease of the microvasculature. Among the earliest pathophysiological events in DN is endothelial dysfunction, which plays a central role in the onset and progression of renal injury. This review presents a comprehensive overview of the molecular mechanisms linking hyperglycemia to endothelial dysfunction, with a focus on oxidative stress, inflammation, and impaired nitric oxide signaling. We further explore the roles of endothelial-derived mediators, glycocalyx degradation, and endothelial-to-mesenchymal transition (EndMT) in aggravating glomerular and peritubular capillary injury. Clinical implications, current diagnostic challenges, and potential biomarkers of endothelial injury are discussed. We highlight emerging therapeutic interventions targeting endothelial pathways, including pharmacological agents, lifestyle interventions, and advanced drug delivery systems. Understanding the vascular underpinnings of DN offers new insights into early diagnosis and renal protection, marking endothelial restoration as a pivotal strategy in managing diabetic kidney disease.

1. Introduction

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus characterized by persistent albuminuria, declining glomerular filtration rate (GFR), and increased cardiovascular morbidity and mortality (Ahmad, 2015; Samsu, 2021). Historically considered a glomerulocentric disease, DN is now increasingly viewed as a consequence of widespread microvascular injury, in which endothelial dysfunction plays a pivotal role. The renal endothelium is essential for vascular homeostasis, filtration barrier integrity, and intercellular communication (Cai et al., 2021). In the diabetic milieu, sustained hyperglycemia leads to structural and functional alterations in the endothelium that culminate in compromised renal function (Efiong et al., 2024; Yang et al., 2024). This review dissects the key mechanisms through which endothelial dysfunction contributes to DN, emphasizing the importance of vascular health in renal protection and highlighting novel therapeutic opportunities.

2. Pathophysiological Mechanisms of Endothelial Dysfunction in DN

The endothelium serves as a dynamic interface regulating vascular tone, permeability, coagulation, and inflammatory

responses (Khaddaj Mallat et al., 2017). In diabetes, chronic hyperglycemia triggers a cascade of molecular events that disrupt endothelial homeostasis (Maamoun et al., 2019). Among the primary mechanisms are increased production of reactive oxygen species (ROS), advanced glycation end-products (AGEs), and activation of protein kinase C (PKC). These processes collectively impair endothelial nitric oxide synthase (eNOS) activity and reduce nitric oxide (NO) bioavailability, a key mediator of vasodilation and anti-inflammatory effects.

Hyperglycemia-induced oxidative stress is a critical driver of endothelial injury (Arcambal et al., 2019). Mitochondrial overproduction of superoxide anions in the setting of high glucose levels promotes oxidative damage to lipids, proteins, and DNA. Concurrently, the accumulation of AGEs and their interaction with the receptor for AGE (RAGE) exacerbate inflammation and endothelial permeability (Snelson et al., 2022; Zhou et al., 2024). In addition, activation of PKC isoforms leads to the upregulation of endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), and proinflammatory cytokines, further destabilizing the endothelial barrier (Zhang et al., 2019).

© The Author(s). 2024 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

3. Glycocalyx Degradation and Vascular Permeability

The endothelial glycocalyx, a carbohydrate-rich layer covering the luminal surface of endothelial cells, is a critical determinant of vascular permeability and mechanotransduction (Fels and Kusche-Vihrog, 2020). In DN, the glycocalyx undergoes enzymatic degradation due to elevated levels of heparanase, hyaluronidase, and oxidative stress (Li et al., 2020; Rabelink et al., 2017). This degradation compromises the endothelial barrier, facilitates albumin leakage, and promotes leukocyte adhesion.

Loss of glycocalyx integrity is particularly evident in glomerular capillaries, where it contributes to proteinuria and glomerulosclerosis (Ermert et al., 2023). The role of syndecan-1, a core protein of the glycocalyx, has been highlighted as both a marker and mediator of endothelial damage (Fernández-Sarmiento et al., 2023; Vahldieck et al., 2023). Experimental studies demonstrate that glycocalyx restoration via exogenous supplementation or inhibition of degrading enzymes can ameliorate renal injury in diabetic models.

4. Endothelial-to-Mesenchymal Transition in Diabetic Nephropathy

Endothelial-to-mesenchymal transition (EndMT) is a process by which endothelial cells lose their characteristic markers (e.g., CD31, VE-cadherin) and acquire mesenchymal features (e.g., α -SMA, fibronectin) (Alvandi and Bischoff, 2021; Piera-Velazquez and Jimenez, 2019). This transition is driven by transforming growth factor- β (TGF- β), inflammatory cytokines, and oxidative stress. In DN, EndMT contributes to peritubular capillary rarefaction, interstitial fibrosis, and progressive renal dysfunction (Jacobs et al., 2024).

Emerging evidence suggests that inhibition of EndMT can preserve peritubular capillaries and prevent fibrotic remodeling (Jacobs et al., 2024). Agents targeting TGF- β signaling, such as fresolimumab or pirfenidone, have shown promise in attenuating EndMT-related fibrosis in preclinical

studies. This highlights EndMT as a potential therapeutic target to halt the progression of DN.

5. Endothelial Biomarkers and Diagnostic Potential

Given the centrality of endothelial dysfunction in DN, identifying reliable biomarkers is crucial for early diagnosis and therapeutic monitoring. Soluble vascular adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and angiopoietin-2 (Ang-2) are elevated in diabetic patients with microalbuminuria and predict progression to overt nephropathy (Theodorakopoulou et al., 2020; Yu et al., 2023). Additionally, circulating levels of endothelial microparticles (EMPs) and syndecan-1 reflect glycocalyx shedding and endothelial stress (Rahbar et al., 2015).

Urinary excretion of endothelial markers, including VEGF and endothelin-1, also provides insights into local vascular injury (Goncharov et al., 2017; Molema et al., 2022). The integration of these biomarkers into clinical practice requires validation across diverse populations and standardization of assay protocols. Advances in omics technologies, particularly proteomics and transcriptomics, offer opportunities for discovering novel endothelial markers linked to diabetic kidney disease.

6. Therapeutic Strategies Targeting Endothelial Dysfunction

Conventional therapies for DN, such as angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs), indirectly benefit endothelial function by reducing glomerular hypertension and inflammation (Alcocer et al., 2023). However, specific strategies targeting endothelial injury are emerging as adjunctive therapies.

Statins, primarily known for lipid-lowering, exhibit pleiotropic effects on the endothelium by enhancing eNOS activity and reducing oxidative stress (Margaritis et al., 2018). Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have

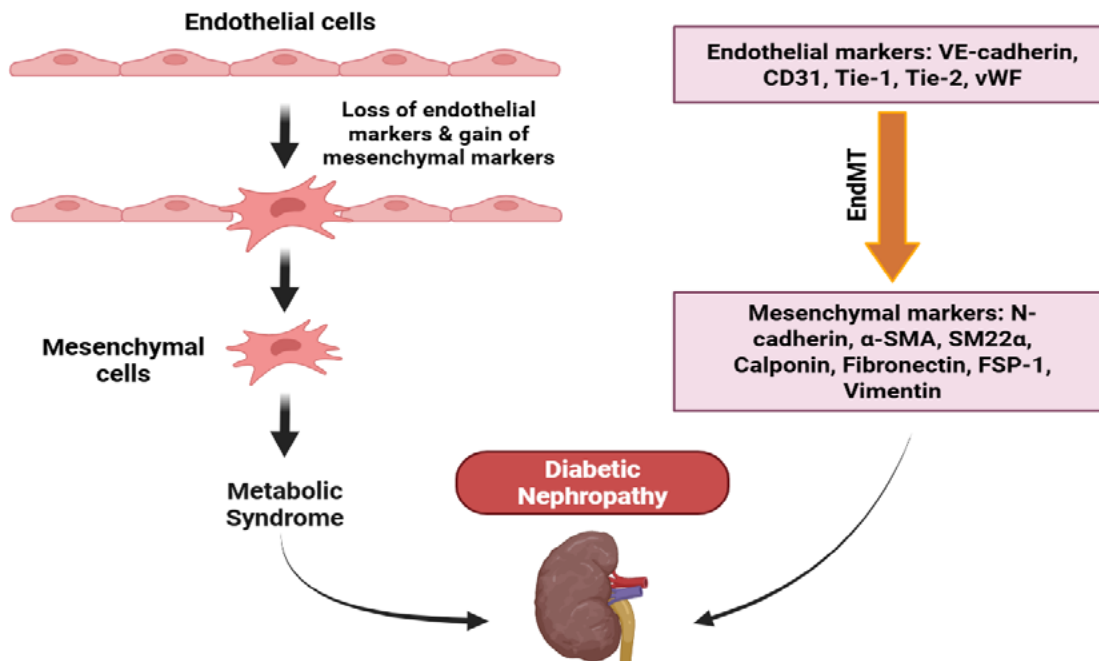


Figure 1: Schematic representation of Endothelial-to-Mesenchymal Transition (EndMT) contributing to Diabetic Nephropathy. Endothelial cells undergo phenotypic transition characterized by the loss of endothelial markers (VE-cadherin, CD31, Tie-1, Tie-2, vWF) and acquisition of mesenchymal markers (N-cadherin, α -SMA, SM22 α , Calponin, Fibronectin, FSP-1, Vimentin). This transition results in the formation of mesenchymal cells, which play a crucial role in the development of metabolic syndrome and the progression of diabetic nephropathy. The diagram illustrates the cellular and molecular changes associated with EndMT in the context of renal pathology.

Table 1: Key Endothelial Biomarkers in Diabetic Nephropathy

Biomarker	Source	Role in DN	Clinical Relevance
sVCAM-1	Endothelial cells	Inflammation, adhesion	Predicts microalbuminuria
sICAM-1	Endothelial cells	Leukocyte adhesion	Correlates with DN severity
Syndecan-1	Glycocalyx shedding	Barrier integrity	Reflects endothelial injury
Angiopoietin-2	Vascular tissue	Angiogenesis, permeability	Linked to progression of DN
Endothelin-1	Endothelium	Vasoconstriction	Elevated in advanced DN

Table 2: Therapeutic Interventions Targeting Endothelial Dysfunction in DN

Intervention	Mechanism of Action	Evidence in DN
ACE inhibitors/ARBs	Reduce glomerular pressure, inflammation	Standard therapy
Statins	Enhance eNOS, reduce oxidative stress	Improve endothelial function
SGLT2 inhibitors	Anti-inflammatory, reduce tubular stress	Improve renal and vascular outcomes
Sulodexide	Glycocalyx restoration	Under clinical investigation
Endothelial Progenitor Cells	Repair damaged endothelium	Promising in preclinical models
NO donors	Enhance vasodilation, reduce oxidative stress	Limited studies in DN

been shown to improve endothelial function independently of glycemic control (Ikonomidis et al., 2020), possibly through reduced tubular workload and inflammation. Additionally, novel agents such as endothelial progenitor cell (EPC) therapies, NO donors, and agents targeting endothelial glycocalyx (e.g., sulodexide) are under investigation.

Lifestyle interventions, including dietary modification, exercise, and smoking cessation, also play an important role in preserving endothelial health. Combining pharmacological and non-pharmacological approaches can synergistically enhance vascular protection and slow the progression of DN.

7. Vascular Crosstalk and Systemic Implications

Endothelial dysfunction in DN is not confined to the kidney. It reflects a systemic vascular pathology that increases the risk of cardiovascular events. Crosstalk between renal and systemic vasculature involves shared mediators such as NO, ET-1, and inflammatory cytokines (Li et al., 2024). Thus, addressing endothelial health in DN has implications beyond renal protection, encompassing broader cardiometabolic benefits. Understanding the interplay between glomerular, peritubular, and systemic endothelial networks is essential for holistic patient management. Targeting common pathways of endothelial injury can mitigate both renal and cardiovascular complications in diabetic individuals.

8. Future Perspectives and Research Directions

Despite significant advances, several gaps remain in our

understanding of endothelial pathology in DN. Further research is needed to delineate the temporal sequence of endothelial injury, identify cell-specific mechanisms, and develop endothelial-targeted therapies with high specificity and minimal side effects. Precision medicine approaches integrating genetic, epigenetic, and biomarker data may enable personalized vascular protection strategies.

Longitudinal studies evaluating endothelial markers alongside clinical outcomes will be crucial in validating their prognostic utility. Moreover, novel drug delivery systems such as nanoparticle-based endothelial-targeted formulations hold promise for enhancing therapeutic efficacy and reducing systemic toxicity.

9. Conclusion

Endothelial dysfunction is a central driver of diabetic nephropathy, bridging metabolic dysregulation with vascular and renal injury. Addressing endothelial health through early diagnosis, targeted therapeutics, and integrated care approaches offers a transformative strategy for mitigating the burden of diabetic kidney disease. Continued research and innovation are essential to translate these insights into clinical impact.

Declarations

Ethics approval statement

No ethical approval was required for the current

study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

Funding

Not Applicable

Author contribution

Conceptualization: D.A, Data curation, Investigation: S.P, M.N.F. Writing—review and editing: P.V.D. All authors have read and agreed to the published version of the manuscript

Acknowledgements

Not Applicable

Reference

- Ahmad, J., 2015. Management of diabetic nephropathy: Recent progress and future perspective. *Diabetes Metab. Syndr. Clin. Res. Rev.* 9, 343–358. <https://doi.org/10.1016/j.dsx.2015.02.008>
- Alcocer, L.A., Bryce, A., De Padua Brasil, D., Lara, J., Cortes, J.M., Quesada, D., Rodriguez, P., 2023. The Pivotal Role of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hypertension Management and Cardiovascular and Renal Protection: A Critical Appraisal and Comparison of International Guidelines. *Am. J. Cardiovasc. Drugs* 23, 663–682. <https://doi.org/10.1007/s40256-023-00605-5>
- Alvandi, Z., Bischoff, J., 2021. Endothelial-Mesenchymal Transition in Cardiovascular Disease. *Arterioscler. Thromb. Vasc. Biol.* 41, 2357–2369. <https://doi.org/10.1161/ATVBAHA.121.313788>
- Arcambal, A., Tailé, J., Rondeau, P., Viranaïcken, W., Meilhac, O., Gonthier, M.-P., 2019. Hyperglycemia modulates redox, inflammatory and vasoactive markers through specific signaling pathways in cerebral endothelial cells: Insights on insulin protective action. *Free Radic. Biol. Med.* 130, 59–70. <https://doi.org/10.1016/j.freeradbiomed.2018.10.430>
- Cai, A., Chatziantoniou, C., Calmont, A., 2021. Vascular Permeability: Regulation Pathways and Role in Kidney Diseases. *Nephron* 145, 297–310. <https://doi.org/10.1159/000514314>
- Efiong, E.E., Bazireh, H., Fuchs, M., Amadi, P.U., Effa, E., Sharma, S., Schmaderer, C., 2024. Crosstalk of Hyperglycaemia and Cellular Mechanisms in the Pathogenesis of Diabetic Kidney Disease. *Int. J. Mol. Sci.* 25, 10882. <https://doi.org/10.3390/ijms252010882>
- Ermert, K., Buhl, E.M., Klinkhammer, B.M., Floege, J., Boor, P., 2023. Reduction of Endothelial Glycocalyx on Peritubular Capillaries in Chronic Kidney Disease. *Am. J. Pathol.* 193, 138–147. <https://doi.org/10.1016/j.ajpath.2022.11.003>
- Fels, B., Kusche-Vihrog, K., 2020. It takes more than two to tango: mechanosignaling of the endothelial surface. *Pflügers Arch. - Eur. J. Physiol.* 472, 419–433. <https://doi.org/10.1007/s00424-020-02369-2>
- Fernández-Sarmiento, J., Molina, C.F., Salazar-Pelaez, L.M., Flórez, S., Alarcón-Forero, L.C., Sarta, M., Hernández-Sarmiento, R., Villar, J.C., 2023. Biomarkers of Glycocalyx Injury and Endothelial Activation are Associated with Clinical Outcomes in Patients with Sepsis: A Systematic Review and Meta-Analysis. *J. Intensive Care Med.* 38, 95–105. <https://doi.org/10.1177/08850666221109186>
- Goncharov, N. V., Nadeev, A.D., Jenkins, R.O., Avdonin, P. V., 2017. Markers and Biomarkers of Endothelium: When Something Is Rotten in the State. *Oxid. Med. Cell. Longev.* 2017. <https://doi.org/10.1155/2017/9759735>
- Ikonomidis, I., Pavlidis, G., Thymis, J., Birba, D., Kalogeris, A., Kousathana, F., Kountouri, A., Balampanis, K., Parissis, J., Andreadou, I., Katogiannis, K., Dimitriadis, G., Bamias, A., Iliodromitis, E., Lambadiari, V., 2020. Effects of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter-2 Inhibitors, and Their Combination on Endothelial Glycocalyx, Arterial Function, and Myocardial Work Index in Patients With Type 2 Diabetes Mellitus After 12-Month Treatme. *J. Am. Heart Assoc.* 9. <https://doi.org/10.1161/JAHA.119.015716>
- Jacobs, M.E., de Vries, D.K., Engelse, M.A., Dumas, S.J., Rabelink, T.J., 2024. Endothelial to mesenchymal transition in kidney fibrosis. *Nephrol. Dial. Transplant.* 39, 752–760. <https://doi.org/10.1093/ndt/gfad238>
- Khaddaj Mallat, R., Mathew John, C., Kendrick, D.J., Braun, A.P., 2017. The vascular endothelium: A regulator of arterial tone and interface for the immune system. *Crit. Rev. Clin. Lab. Sci.* 54, 458–470. <https://doi.org/10.1080/10408363.2017.1394267>
- Li, M., Armelloni, S., Mattinzoli, D., Ikehata, M., Chatziantoniou, C., Alfieri, C., Molinari, P., Chadichristos, C.E., Malvica, S., Castellano, G., 2024. Crosstalk mechanisms between glomerular endothelial cells and podocytes in renal diseases and kidney transplantation. *Kidney Res. Clin. Pract.* 43, 47–62. <https://doi.org/10.23876/j.krcp.23.071>
- Li, Z., Wu, N., Wang, J., Zhang, Q., 2020. Roles of Endovascular Calyx Related Enzymes in Endothelial Dysfunction and Diabetic Vascular Complications. *Front. Pharmacol.* 11. <https://doi.org/10.3389/fphar.2020.590614>
- Maamoun, H., Abdelsalam, S.S., Zeidan, A., Korashy, H.M., Agouni, A., 2019. Endoplasmic Reticulum Stress: A Critical Molecular Driver of Endothelial Dysfunction and Cardiovascular Disturbances Associated with Diabetes. *Int. J. Mol. Sci.* 20, 1658. <https://doi.org/10.3390/ijms20071658>
- Margaritis, M., Sanna, F., Antoniadis, C., 2018. Statins and Oxidative Stress in the Cardiovascular System. *Curr. Pharm. Des.* 23, 7040–7047. <https://doi.org/10.2174/1381612823666170926130338>
- Molema, G., Zijlstra, J.G., van Meurs, M., Kamps, J.A.A.M., 2022. Renal microvascular endothelial cell responses in sepsis-induced acute kidney injury. *Nat. Rev. Nephrol.* 18, 95–112. <https://doi.org/10.1038/s41581-021-00489-1>
- Piera-Velazquez, S., Jimenez, S.A., 2019. Endothelial to Mesenchymal Transition: Role in Physiology and in the Pathogenesis of Human Diseases. *Physiol. Rev.* 99, 1281–1324. <https://doi.org/10.1152/physrev.00021.2018>
- Rabelink, T.J., van den Berg, B.M., Garsen, M., Wang, G., Elkin, M., van der Vlag, J., 2017. Heparanase: roles in cell survival, extracellular matrix remodelling and the development of kidney disease. *Nat. Rev. Nephrol.* 13, 201–212. <https://doi.org/10.1038/nrneph.2017.6>
- Rahbar, E., Cardenas, J.C., Baimukanova, G., Usadi, B., Bruhn, R., Pati, S., Ostrowski, S.R., Johansson, P.I., Holcomb, J.B., Wade, C.E., 2015. Endothelial glycocalyx shedding and vascular permeability in severely injured trauma patients. *J. Transl. Med.* 13, 117. <https://doi.org/10.1186/s12967-015-0481-5>
- Samsu, N., 2021. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. *Biomed Res. Int.*

- 2021, 1–17. <https://doi.org/10.1155/2021/1497449>
23. Snelson, M., Lucut, E., Coughlan, M.T., 2022. The Role of AGE-RAGE Signalling as a Modulator of Gut Permeability in Diabetes. *Int. J. Mol. Sci.* 23, 1766. <https://doi.org/10.3390/ijms23031766>
 24. Theodorakopoulou, M.P., Schoina, M., Sarafidis, P., 2020. Assessment of Endothelial and Microvascular Function in CKD: Older and Newer Techniques, Associated Risk Factors, and Relations with Outcomes. *Am. J. Nephrol.* 51, 931–949. <https://doi.org/10.1159/000512263>
 25. Vahldieck, C., Cianflone, E., Fels, B., Löning, S., Depelmann, P., Sabatino, J., Salerno, N., Karsten, C.M., Torella, D., Weil, J., Sun, D., Goligorsky, M.S., Kusche-Vihrog, K., 2023. Endothelial Glycocalyx and Cardiomyocyte Damage Is Prevented by Recombinant Syndecan-1 in Acute Myocardial Infarction. *Am. J. Pathol.* 193, 474–492. <https://doi.org/10.1016/j.ajpath.2022.12.009>
 26. Yang, D.-R., Wang, M.-Y., Zhang, C.-L., Wang, Y., 2024. Endothelial dysfunction in vascular complications of diabetes: a comprehensive review of mechanisms and implications. *Front. Endocrinol. (Lausanne)*. 15. <https://doi.org/10.3389/fendo.2024.1359255>
 27. Yu, H., Song, Y.-Y., Li, X.-H., 2023. Early diabetic kidney disease: Focus on the glycocalyx. *World J. Diabetes* 14, 460–480. <https://doi.org/10.4239/wjd.v14.i5.460>
 28. Zhang, J., Wang, Y.-J., Wang, X., Xu, L., Yang, X.-C., Zhao, W.-S., 2019. PKC-Mediated Endothelin-1 Expression in Endothelial Cell Promotes Macrophage Activation in Atherogenesis. *Am. J. Hypertens.* 32, 880–889. <https://doi.org/10.1093/ajh/hpz069>
 29. Zhou, M., Zhang, Y., Shi, L., Li, L., Zhang, D., Gong, Z., Wu, Q., 2024. Activation and modulation of the AGEs-RAGE axis: Implications for inflammatory pathologies and therapeutic interventions – A review. *Pharmacol. Res.* 206, 107282. <https://doi.org/10.1016/j.phrs.2024.107282>