Review

Discovery Medicine 2026; 38(206): 670–675
https://doi.org/10.24976/Discov.Med.202638206.55

Research Progress on the Apelin Receptor and Its Endogenous Ligands in Hypertension Development

Qiaozhen Tian[1], Fangfang Wang[1], Xiaojing Yu[2], Shuhuan Tang[2], Yuming Kang[2,*]

[1]Institute of Brain Science, School of Medicine, Shanxi Datong University, 037009 Datong, Shanxi, China
[2]Shaanxi Province Engineering Technology Research Center for New Therapeutic Vaccines, Xi'an Jiaotong University, 710049 Xi'an, Shaanxi, China
*Correspondence: ykang@mail.xjtu.edu.cn (Yuming Kang)

Submitted: 30 December 2025 Revised: 16 January 2026 Accepted: 11 February 2026 Published: 20 March 2026

Apelin receptor (APJ) is a G protein-coupled receptor whose endogenous ligands include Apelin and Elabela (ELA), forming the Apelin/APJ and ELA/APJ signaling axes. Recent studies have shown that Apelin and ELA play a critical regulatory role in the development of hypertension through mechanisms such as modulating vascular tone, exerting anti-inflammatory and antioxidant effects, and inhibiting the renin-angiotensin-aldosterone system (RAAS). This article systematically reviews the mechanisms of the Apelin/APJ and ELA/APJ systems in hypertension, focusing on their effects on vascular endothelial function, smooth muscle proliferation, RAAS regulation, oxidative stress, and inflammatory responses. It further explores their potential as novel therapeutic targets for hypertension, aiming to provide a theoretical basis for understanding the pathogenesis of hypertension and for the development of new antihypertensive drugs.

Keywords: APJ; Apelin; Elabela; hypertension; research progress

Introduction

Hypertension, one of the most prevalent cardiovascular diseases worldwide, serves as a major risk factor for cardiovascular events such as coronary heart disease, stroke, and heart failure [1,2]. Although a variety of antihypertensive drugs are available for clinical use, the pathogenesis of hypertension remains incompletely understood, and some patients still experience refractory hypertension or adverse drug reactions [3,4]. Consequently, exploring novel therapeutic targets and regulatory mechanisms is of great significance. The Apelin receptor (APJ) is an orphan G protein-coupled receptor, with endogenous ligands including Apelin and Elabela (ELA) [5]. In recent years, the functions of the Apelin/APJ and ELA/APJ systems in the cardiovascular system have been increasingly elucidated, demonstrating important physiological and pathological roles, particularly in blood pressure regulation, vascular remodeling, anti-inflammatory responses, and antioxidant effects [6,7]. This review integrates the latest research advances to systematically summarize the mechanisms by which APJ and its endogenous ligands contribute to the development and progression of hypertension, and to discusses their potential as therapeutic targets.

Molecular Biological Basis of APJ and Its Endogenous Ligands

Apelin Receptor (APJ)

The APJ receptor is encoded by the APLNR gene located on human chromosome 11q12.1. Its protein product consists of 380 amino acid residues and features a classic seven-transmembrane domain structure, belonging to the G protein-coupled receptor (GPCR) family [8]. Although APJ has similarities in distribution patterns and amino acid compositions with the angiotensin II type 1 receptor (AT1R), it exhibits no affinity for Ang II [9]. APJ is widely expressed in eukaryotes and is present in a broad range of human embryonic and adult tissues [10,11]. Ma *et al.* [12] reported the crystal structure of the human apelin-17-APJ complex, revealing that apelin-17 adopts a lactam-constrained, curved conformation and engages the receptor via a two-site binding mode. Functionally, human genetic studies have linked polymorphisms in the APLNR gene (encoding APJ) to the occurrence of coronary artery disease (CAD) and hypertension [13], underscoring its critical role in cardiovascular pathophysiology.

Apelin

Apelin was first identified in 1998 by Tatemoto *et al.* [9] as the initial endogenous ligand of APJ, isolated from bovine gastric secretions using reverse pharmacology. In humans, the apelin gene (APLN) is located on chromosome Xq25–26.1 [14]. The gene encodes a 77-amino-

acid precursor protein, which undergoes post-translational processing and can be proteolytically cleaved into multiple bioactive C-terminal fragments. These fragments include Apelin-36, Apelin-17, Apelin-13, and its N-terminal pyroglutamylated form, Pyr-apelin-13, among others [15]. All active isoforms share a highly conserved 12-amino-acid core sequence at their C-terminus, which is essential for binding to the APJ receptor [16].

Elabela

Recent studies have revealed that Apelin knockout (KO) mice and APJ KO mice exhibit distinct cardiovascular phenotypes, suggesting the presence of another endogenous ligand for APJ that exerts effects on the cardiovascular system. Elabela (ELA), also known as Toddler, was identified in 2013 as the second endogenous ligand of APJ [17,18]. The human ELA gene encodes a prohormone consisting of 54 amino acids. This precursor undergoes enzymatic processing in the endoplasmic reticulum, sequentially yielding Elabela-54, Elabela-32, and Elabela-22, before finally being cleaved by furin to produce the evolutionarily conserved 11-peptide form, Elabela-11 [19]. The C-terminal 13 amino acids are highly conserved across vertebrates and constitute the core region responsible for receptor binding and functional activity [20].

Unlike Apelin, Elabela is widely expressed in human embryonic stem cells and primitive gut tissues, where it regulates cell migration and differentiation in the endoderm and mesoderm, thereby playing a crucial role in cardiac development [21]. Through both paracrine signaling and systemic circulation, Elabela modulates fetal heart development, maternal blood pressure, renal function, and proper placental formation during pregnancy [22,23]. Research has shown that Elabela is expressed in both normal and preeclamptic placental tissues. In adult tissues, it is primarily expressed in the kidneys, where it exhibits anti-inflammatory, anti-apoptotic, and anti-fibrotic properties. It protects the kidneys and cultured renal cells from DNA damage response (DDR) and ischemia-reperfusion (I/R) injury. Elabela-32 and Elabela-11 are considered potential therapeutic agents for renal I/R injury and acute kidney injury (AKI) due to their protective effects against inflammation, apoptosis, and fibrosis [24]. Within the cardiovascular system, Elabela is predominantly located in vascular endothelial cells and fibroblasts, contributing to cardiovascular homeostasis and demonstrating significant pathophysiological relevance [25,26].

Role of the Apelin/APJ System in Hypertension

The Apelin/APJ system has been implicated in blood pressure regulation, with evidence suggesting its involvement in hypertension pathogenesis. In a study using the deoxycorticosterone acetate (DOCA)-salt hypertensive rat model, both Apelin and APJ mRNA expression levels were significantly reduced compared to the control group [27]. Administration of exogenous Apelin decreased blood pressure by inhibiting the renin-angiotensin-aldosterone system (RAAS), supporting its antihypertensive role and elucidating the underlying mechanisms.

This association is further supported by evidence from experimental and clinical studies. A meta-analysis of 10 studies involving 2715 subjects demonstrated that circulating apelin levels were significantly lower in hypertensive patients compared to healthy controls (WMD = –39.85 pg/mL, 95% CI: –65.56 to –14.15; $p = 0.002$); this inverse association was particularly evident in Caucasian populations and hospital-based studies [28]. Similarly, multiple clinical studies have reported reduced serum apelin levels in essential hypertension, correlating with increased blood pressure variability and hypertension risk [29–31]. Serinkan *et al*. [32] demonstrated that elderly hypertensive patients exhibited lower serum Apelin expression levels compared to age-matched normotensive controls. Moreover, lower serum Apelin levels were associated with increased variability in blood pressure parameters, including 24-hour systolic and diastolic standard deviations, as well as daytime systolic and diastolic coefficient of variation. Wu *et al*. [33] investigated the role of genetic factors in hypertension pathogenesis and found that the rs10501367 polymorphism of the APJ gene reduced the risk of hypertension in male patients, highlighting the biological relevance of the Apelin/APJ system in the regulation of blood pressure. Multiple clinical studies have consistently indicated that Apelin acts as a protective factor against hypertension and may serve as an indicator for evaluating the efficacy of antihypertensive drugs [34].

The mechanisms by which the Apelin/APJ system regulates hypertension are multifaceted, involving several pathways. Angiotensin II (Ang II), a key component of RAAS, exerts potent vasoconstrictive effects, increases aldosterone secretion, promotes water and sodium retention, and contributes to the onset and progression of hypertension [35]. Additionally, central RAAS plays a crucial role in raising blood pressure, as Ang II reduces nitric oxide (NO) bioavailability, promotes reactive oxygen species (ROS) generation, and enhances sympathetic nervous system activity, collectively contributing to the development of hypertension. Apelin counteracts these effects by antagonizing RAAS, specifically by reducing angiotensin-converting enzyme (ACE) activity, downregulating AT1R expression, and promoting ACE2/Ang-(1-7)/Mas receptor axis activity, thereby attenuating Ang II–mediated vasoconstriction and oxidative stress. The Apelin/APJ system is highly expressed in vascular endothelium, where Apelin promotes NO release from endothelial cells, leading to vasodilation of smooth muscle cells and subsequent blood pressure reduction [36]. Luo *et al*. [37] demonstrated that the use of nitric oxide synthase inhibitors could attenuate Apelin-induced blood pressure reduction, suggesting that Apelin binding

to APJ receptors stimulates NO production via nitric oxide synthase activation. Further studies have confirmed that Apelin achieves its antihypertensive effects through the vascular endothelial pathway, a mechanism closely associated with APJ and endothelial nitric oxide synthase. Under conditions of intact and functional vascular endothelium, Apelin enhances the activity of endothelial nitric oxide synthase in a concentration-dependent manner, increasing NO production and release to reduce blood pressure [38]. In summary, as an endogenous bioactive peptide, Apelin regulates hypertension by antagonizing RAAS and modulating vascular endothelial pathways, ultimately contributing to blood pressure reduction. These findings highlight Apelin as a potential therapeutic target for the development of novel antihypertensive drugs.

Role of the Elabela/APJ System in Hypertension

The Elabela/APJ system plays a protective role in hypertension through multiple mechanisms, including modulation of vascular tone, inhibition of the renin-angiotensin system (RAS), and anti-inflammatory effects. This section examines its role in clinical hypertension, animal models, salt-sensitive hypertension, and hypertensive disorders of pregnancy.

The ELA/APJ axis plays a crucial role in regulating blood pressure. Studies examining ELA/APJ expression in hypertensive patients and animal models indicate that this axis modulates vascular tone during the early stages of hypertension, highlighting its predictive and therapeutic potential [39]. Li *et al.* [40] observed significantly lower ELA levels in newly diagnosed hypertensive individuals compared to healthy controls, with ELA levels progressively declining as blood pressure increased. ELA levels positively correlated with flow-mediated vasodilation but showed no significant association with brachial-ankle pulse wave velocity, suggesting that ELA may serve as a biomarker of impaired vasodilatory function in hypertension. Wang *et al.* [41] further reported that ELA-induced vasodilation is independent of endothelial cells and nitric oxide (NO), indicating that the precise mechanism through which ELA modulates vascular function in hypertension warrants further investigation.

Animal studies demonstrate that sustained administration of exogenous ELA or ELA gene therapy can effectively attenuate blood pressure elevation in hypertensive mouse models by modulating the renin-angiotensin system (RAS), a key pathway in hypertension pathogenesis that regulates blood pressure, electrolyte balance, and internal homeostasis. In addition, ELA reduces the expression of forkhead box protein M1, leading to decreased transcription of angiotensin-converting enzyme (ACE) [34]. In Ang II-infused mice, ELA administration has been shown to alleviate hypertension-associated pathological cardiac remodeling and dysfunction. The protective mechanisms extend beyond blood pressure modulation, encompassing the attenuation of myocardial hypertrophy, fibrosis, and endothelial ferroptosis. These effects are potentially mediated through the suppression of cardiac interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling and the activation of the cystine/glutamate antiporter (xCT)/glutathione peroxidase 4 (GPX4) antioxidant pathway [42]. Xu *et al.* [43] further confirmed the inhibitory effect of ELA on the RAS in a rat hypertension model, demonstrating that ELA not only lowered blood pressure but also exhibited a protective effect on distal renal units. Specifically, ELA reduces blood pressure in hypertensive model rats by modulating the ACE/ACE2 balance and regulating the protein kinase B (Akt)/YAP signaling pathway, thereby exerting anti-apoptotic effects and mitigating fibrotic remodeling [44].

Salt-sensitive hypertension refers to the physiological phenomenon in which blood pressure fluctuates with salt intake, rising with excessive consumption and falling with restriction [45,46]. Elabela exhibits antihypertensive effects in salt-sensitive hypertension while also suppressing renal inflammation, fibrosis, and injury. Elabela-32 notably suppresses intrarenal RAS activation, characterized by downregulation of renal medullary (pro)renin receptor and renin expression, as well as reduced urinary excretion of AngII and prorenin/renin [47]. Peripheral Elabela may prevent salt-sensitive hypertension by inhibiting the intrarenal RAS and the NADPH oxidase/reactive oxygen species (ROS)/NLRP3 inflammasome pathway [48]. Schreiber *et al.* [49] employed continuous infusion of AAV9 vectors carrying the ELA gene in rats to study ELA distribution under high-salt diet conditions and its relationship with salt-induced hypertension. After three months of high-salt feeding, ELA was predominantly localized in the renal collecting ducts. By the seventh week, the ELA-treated group showed a gradual decline in blood pressure, increased excretion of sodium and chloride, and reduced glomerular and tubulointerstitial damage compared to controls, indicating that ELA delays hypertension onset, preserves glomerular integrity, and suppresses renal fibrosis along with related gene expression. Post-transcriptional processing of ELA generates splice variants of varying lengths, including ELA11, ELA14, ELA22, and ELA32. Among these, ELA14 and mature ELA32 exhibit comparable efficacy in suppressing iodixanol-induced oxidative stress and inflammatory responses, suggesting that ELA14 may serve as a key therapeutic peptide for cardiorenal diseases, potentially replacing ELA32 [50].

Furthermore, ELA has been implicated in hypertensive disorders of pregnancy [51]. Preeclampsia, characterized by elevated blood pressure and proteinuria, poses serious risks to maternal and fetal health and is a leading cause of morbidity and mortality [52,53]. In animal studies, Ho *et al.* [54] observed that ELA knockout in

pregnant mice resulted in placental hypoplasia, manifested as thinner labyrinthine layers and reduced placental volume. Some pregnant mice also exhibited severe embryonic cardiovascular malformations, fetal growth restriction, and preeclampsia-like symptoms such as hypertension and proteinuria, which were alleviated by ELA treatment.

Previous research indicates that ELA plays an essential functional role in both normal pregnancy and preeclampsia. Compared to non-pregnant women, pregnant women show elevated serum ELA levels that remain high throughout gestation, demonstrating a pregnancy stage-dependent pattern [55]. ELA also contributes to vasodilation and reduces diastolic pressure [43]. Recent studies reveal that ELA is primarily expressed in placental villous trophoblasts. In pregnancies complicated by hypertensive disorders, impaired early placental development and reduced trophoblast invasion are associated with decreased ELA expression and disrupted placental function [56]. Furthermore, ELABELA plasma concentrations are higher in patients with late-onset preeclampsia than in those with a normal pregnancy. However, women with early-onset preeclampsia have similar ELABELA plasma concentrations to those with a normal pregnancy [57]. Conversely, severe preeclampsia is associated with reduced ELA expression. Recent experiments indicate that diminished ELA expression weakens cell migration and invasion capacities [51,58]. Moreover, ELA reduces pAKT levels in Bewo cells, suggesting that ELA may participate in trophoblast invasion and the pathogenesis of preeclampsia by modulating the AKT signaling pathway [59]. These findings collectively highlight ELA as a potential novel biomarker for the clinical screening of preeclampsia [60].

Despite promising findings, several limitations should be acknowledged. Most evidence derives from animal models or observational human studies, and causal mechanisms in human hypertension remain to be fully elucidated. The competitive and potentially opposing effects of apelin and ELA under different pathophysiological conditions require further exploration. Future research should prioritize the development of selective APJ agonists or biased ligands, the establishment of longitudinal clinical cohorts to validate ELA and apelin as biomarkers, and mechanistic studies to clarify their roles in resistant hypertension and hypertension-associated organ damage.

Conclusion

In summary, the Apelin/APJ and Elabela/APJ systems regulate blood pressure through mechanisms, including RAAS antagonism, endothelial NO release, vascular smooth muscle modulation, and anti-inflammatory effects. Although evidence from both animal and clinical studies supports their protective roles in hypertension, several questions remain regarding their precise signaling pathways, tissue-specific functions, and therapeutic potential. Future research should focus on elucidating the differential effects of apelin and ELA, developing targeted agonists or modulators, and conducting longitudinal clinical studies to validate their utility as biomarkers or therapeutic targets in hypertension and related cardiovascular disorders.

Availability of Data and Materials

Not applicable.

Author Contributions

QT and YK designed the research study. QT and FW performed the research. QT, XY and ST analyzed the data. QT drafted the initial manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This review was supported by the Youth Project of Basic Research Program of Shanxi Provincial Department of Science and Technology (No.202203021212491), Shanxi Provincial Colleges and Universities Science and Technology Innovation Project (No. 2021L400), Shanxi Datong University Doctoral Research Start-up Project (No. 2018-B-36); National Natural Science Foundation of China (No. 82370437, 82470458, 82270468).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Chen X, Yan D, Liu C, Dai J, Li Z, Lu Y. The trend analysis and comparison of pulmonary arterial hypertension disease burden in China and India from 1990 to 2021: a study based on the Global Burden of Disease 2021 database. European Journal of Medical Research. 2025; 31: 78. https://doi.org/10.1186/s40001-025-03489-0.

[2] Kario K. Implementation hypertension: a new paradigm for global hypertension control in the JSH 2025, WHO 2025, and AHA/ACC 2025 guideline era. Hypertension Research. 2026; 49: 1–6. https://doi.org/10.1038/s41440-025-02497-1.

[3] Filippone EJ, Naccarelli GV, Foy AJ. Controversies in Hypertension V: Resistant and Refractory Hypertension. The American Journal of Medicine. 2024; 137: 12–22. https://doi.org/10.1016/j.amjmed.2023.09.015.

[4] Yao K, Bai Y, Kang X, Zhang Y, Qiao J. Trends in the prevalence of apparent treatment-resistant hypertension among U.S. adults, 1999-2018. American Journal of Preventive Cardiology. 2025; 24: 101360. https://doi.org/10.1016/j.ajpc.2025.101360.

[5] Gao S, Chen H. Therapeutic potential of apelin and Elabela in cardiovascular disease. Biomedicine & Pharmacotherapy. 2023; 166: 115268. https://doi.org/10.1016/j.biopha.2023.115268.

[6] Li S, Yuan S, Yang S, Zhou C, Zhong Y, Huang Z, *et al*. Apelin-13/APJ promotes neural stem cells to repair ischemic stroke. Tissue & Cell. 2025; 95: 102872. https://doi.org/10.1016/j.tice.2025.102872.

[7] Naldi L, Peri A, Fibbi B. Apelin/APJ: Another Player in the Cancer Biology Network. International Journal of Molecular Sciences. 2025; 26: 2986. https://doi.org/10.3390/ijms26072986.

[8] Wagenaar GTM, Moll GN. Advances in the therapeutic potentials of ligands of the apelin receptor APJ. European Journal of Pharmacology. 2025; 991: 177302. https://doi.org/10.1016/j.ejphar.2025.177302.

[9] Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, *et al*. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochemical and Biophysical Research Communications. 1998; 251: 471–476. https://doi.org/10.1006/bbrc.1998.9489.

[10] Marczewski K, Gospodarczyk N, Gospodarczyk A, Widuch M, Tkocz M. APELIN IN HEART FAILURE. Wiadomosci Lekarskie. 2022; 75: 2501–2506. https://doi.org/10.36740/WLek202210130.

[11] Kidoya H, Naito H, Muramatsu F, Yamakawa D, Jia W, Ikawa M, *et al*. APJ Regulates Parallel Alignment of Arteries and Veins in the Skin. Developmental Cell. 2015; 33: 247–259. https://doi.org/10.1016/j.devcel.2015.02.024.

[12] Ma Y, Yue Y, Ma Y, Zhang Q, Zhou Q, Song Y, *et al*. Structural Basis for Apelin Control of the Human Apelin Receptor. Structure. 2017; 25: 858–866.e4. https://doi.org/10.1016/j.str.2017.04.008.

[13] Yu XH, Tang ZB, Liu LJ, Qian H, Tang SL, Zhang DW, *et al*. Apelin and its receptor APJ in cardiovascular diseases. Clinica Chimica Acta. 2014; 428: 1–8. https://doi.org/10.1016/j.cca.2013.09.001.

[14] Agarwala Y, Sharma R. The role of apelin in cancer. Frontiers in Oncology. 2025; 15: 1683865. https://doi.org/10.3389/fonc.2025.1683865.

[15] Pisarenko OI, Studneva IM. Apelin C-Terminal Fragments: Biological Properties and Therapeutic Potential. Biochemistry. Biokhimiia. 2023; 88: 1874–1889. https://doi.org/10.1134/S0006297923110160.

[16] Erdem H, Yıldırım O, Kalkışım K, Aydın HR, Kaşko Arıcı Y, Kaya Korkmaz Ö, *et al*. Importance of Apelin in Prostate Hyperplasia and Effects of 5 Alpha Reductase on this Mechanism. Archivos Espanoles De Urologia. 2025; 78: 995–1001. https://doi.org/10.56434/j.arch.esp.urol.20257808.130.

[17] Chng SC, Ho L, Tian J, Reversade B. ELABELA: a hormone essential for heart development signals via the apelin receptor. Developmental Cell. 2013; 27: 672–680. https://doi.org/10.1016/j.devcel.2013.11.002.

[18] Pauli A, Norris ML, Valen E, Chew GL, Gagnon JA, Zimmerman S, *et al*. Toddler: an embryonic signal that promotes cell movement via Apelin receptors. Science. 2014; 343: 1248636. https://doi.org/10.1126/science.1248636.

[19] Rubattu S. Elabela Peptide: A New Player in Hypertension and Vascular Damage. High Blood Pressure & Cardiovascular Prevention. 2023; 30: 5–6. https://doi.org/10.1007/s40292-022-00556-z.

[20] Shin K, Kenward C, Rainey JK. Apelinergic System Structure and Function. Comprehensive Physiology. 2017; 8: 407–450. https://doi.org/10.1002/cphy.c170028.

[21] Yan P, Meng C, Yang S, Huang W, Wang T. ELABELA: a polypeptide with therapeutic potential in cardiovascular diseases. Frontiers in Cardiovascular Medicine. 2025; 12: 1623215. https://doi.org/10.3389/fcvm.2025.1623215.

[22] Qi Y, Hou Y, Ma M, Li X, Wu J. Circulating levels of Elabela in pregnant women with missed abortion. Gynecological Endocrinology. 2022; 38: 693–696. https://doi.org/10.1080/09513590.2022.2090539.

[23] Hendrianus, Adiarto S, Prakoso R, Firdaus I, Indriani S, Rudiktyo E, *et al*. A Novel Peptide Elabela is Associated with Hypertension-Related Subclinical Atherosclerosis. High Blood Pressure & Cardiovascular Prevention. 2023; 30: 37–44. https://doi.org/10.1007/s40292-022-00554-1.

[24] Chen H, Wang L, Wang W, Cheng C, Zhang Y, Zhou Y, *et al*. ELABELA and an ELABELA Fragment Protect against AKI. Journal of the American Society of Nephrology. 2017; 28: 2694–2707. https://doi.org/10.1681/ASN.2016111210.

[25] Dawid M, Mlyczyńska E, Jurek M, Respekta N, Pich K, Kurowska P, *et al*. Apelin, APJ, and ELABELA: Role in Placental Function, Pregnancy, and Foetal Development-An Overview. Cells. 2021; 11: 99. https://doi.org/10.3390/cells11010099.

[26] Hanssens S, Marousez L, Pécheux O, Besengez C, Storme L, Deruelle P, *et al*. Maternal obesity reduces apelin level in cord blood without altering the placental apelin/elabela-APJ system. Placenta. 2022; 128: 112–115. https://doi.org/10.1016/j.placenta.2022.09.011.

[27] Kursunluoglu-Akcilar R, Kilic-Toprak E, Kilic-Erkek O, Turgut S, Bor-Kucukatay M. Apelin-induced hemorheological alterations in DOCA-salt hypertensive rats. Clinical Hemorheology and Microcirculation. 2014; 56: 75–82. https://doi.org/10.3233/CH-121649.

[28] Xie H, Luo G, Zheng Y, Hu D, Peng F, Xie L. Lowered circulating apelin is significantly associated with an increased risk for hypertension: A meta-analysis. Clinical and Experimental Hypertension. 2017; 39: 435–440. https://doi.org/10.1080/10641963.2016.1267199.

[29] Wen J, Li X. Effect of Magnesium Sulfate Combined with Phentolamine and Nifedipine for Gestational Hypertension and Serum Levels of LIF and Apelin. Journal of the College of Physicians and Surgeons–Pakistan. 2019; 29: 231–234. https://doi.org/10.29271/jcpsp.2019.03.231.

[30] Rostamzadeh F, Najafipour H, Yazdani R, Nakhaei S, Alinaghi Langari A. Changes in serum levels of apelin and nitric oxide in hospitalized patients with COVID-19: association with hypertension, diabetes, obesity, and severity of disease. European Journal of Medical Research. 2022; 27: 243. https://doi.org/10.1186/s40001-022-00852-3.

[31] Jafari S, Moazenzadeh M, Jangipour Afshar P, Nasri H. Comparison of Serum proBNP and Apelin Levels in Hypertensive Crisis Versus Controlled Hypertension: Impact of Opium Addiction Status. Addiction & Health. 2025; 17: 1581. https://doi.org/10.34172/ahj.1581.

[32] Serinkan Cinemre FB, Cinemre H, Bahtiyar N, Kahyaoğlu B, Ağaç MT, Shundo H, *et al*. Apelin, Omentin-1, and Vaspin in patients with essential hypertension: association of adipokines with trace elements, inflammatory cytokines, and oxidative damage markers. Irish Journal of Medical Science. 2021; 190: 97–106. https://doi.org/10.1007/s11845-020-02272-w.

[33] Wu XD, Zhang N, Liang M, Liu WL, Lin BB, Xiao YR, *et al*. Gender-specific association between Apelin/APJ gene polymorphisms and hypertension risk in Southeast China. Gene. 2018; 669: 63–68. https://doi.org/10.1016/j.gene.2018.05.079.

[34] Rozwadowski J, Borodzicz-Jażdżyk S, Czarzasta K, Cudnoch-Jędrzejewska A. A Review of the Roles of Apelin and ELABELA Peptide Ligands in Cardiovascular Disease, Including Heart Failure and Hypertension. Medical Science Monitor.

2022; 28: e938112. https://doi.org/10.12659/MSM.938112.

[35] Erichsen L, Kloss LDF, Thimm C, Bohndorf M, Schichel K, Wruck W, *et al*. Derivation of the Immortalized Cell Line UM51-PrePodo-hTERT and Its Responsiveness to Angiotensin II and Activation of the RAAS Pathway. Cells. 2023; 12: 342. https://doi.org/10.3390/cells12030342.

[36] Sabouri M, Norouzi J, Zarei Y, Sangani MH, Hooshmand Moghadam B. Comparing High-Intensity Interval Training (HIIT) and Continuous Training on Apelin, APJ, NO, and Cardiotrophin-1 in Cardiac Tissue of Diabetic Rats. Journal of Diabetes Research. 2020; 2020: 1472514. https://doi.org/10.1155/2020/1472514.

[37] Luo X, Liu J, Zhou H, Chen L. Apelin/APJ system: A critical regulator of vascular smooth muscle cell. Journal of Cellular Physiology. 2018; 233: 5180–5188. https://doi.org/10.1002/jcp.26339.

[38] Huang M, Chang J, Liu Y, Yin J, Zeng X. Apelin/APJ alleviates diabetic nephropathy by improving glomerular endothelial cells dysfunction via SIRT3 KLF15. Molecular Medicine Reports. 2025; 31: 122. https://doi.org/10.3892/mmr.2025.13487.

[39] Song J, Tang J, Zhang Z, Liu Y, Zhong J. Targeting the elabela/apelin-apelin receptor axis as a novel therapeutic approach for hypertension. Chinese Medical Journal. 2022; 135: 1019–1026. https://doi.org/10.1097/CM9.0000000000001766.

[40] Li Y, Yang X, Ouyang S, He J, Yu B, Lin X, *et al*. Declined circulating Elabela levels in patients with essential hypertension and its association with impaired vascular function: A preliminary study. Clinical and Experimental Hypertension. 2020; 42: 239–243. https://doi.org/10.1080/10641963.2019.1619756.

[41] Wang Z, Yu D, Wang M, Wang Q, Kouznetsova J, Yang R, *et al*. Elabela-apelin receptor signaling pathway is functional in mammalian systems. Scientific Reports. 2015; 5: 8170. https://doi.org/10.1038/srep08170.

[42] Zhang Z, Tang J, Song J, Xie M, Liu Y, Dong Z, *et al*. Elabela alleviates ferroptosis, myocardial remodeling, fibrosis and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling. Free Radical Biology & Medicine. 2022; 181: 130–142. https://doi.org/10.1016/j.freeradbiomed.2022.01.020.

[43] Xu C, Wang F, Chen Y, Xie S, Sng D, Reversade B, *et al*. ELABELA antagonizes intrarenal renin-angiotensin system to lower blood pressure and protects against renal injury. American Journal of Physiology. Renal Physiology. 2020; 318: F1122–F1135. https://doi.org/10.1152/ajprenal.00606.2019.

[44] Xi Y, Li Y, Ren W, Bo W, Ma Y, Pan S, *et al*. ELABELA-APJ-Akt/YAP Signaling Axis: A Novel Mechanism of Aerobic Exercise in Cardioprotection of Myocardial Infarction Rats. Medicine and Science in Sports and Exercise. 2023; 55: 1172–1183. https://doi.org/10.1249/MSS.0000000000003143.

[45] Chrysant SG. A Pathophysiologic Mechanism for the Treatment of Salt-Sensitive Hypertension and Heart Failure: The Role of β-Arrestins. Clinical Drug Investigation. 2026; 46: 49–55. https://doi.org/10.1007/s40261-025-01495-y.

[46] Siakabanze C, Luwaya E, Muchaili L, Siame L, Sibbenga F, Tande M, *et al*. Integrated mechanisms linking sodium-potassium imbalance to salt-sensitive hypertension. Physiological Reports. 2025; 13: e70715. https://doi.org/10.14814/phy2.70715.

[47] Sainsily X, Coquerel D, Giguère H, Dumont L, Tran K, Noll C, *et al*. Elabela Protects Spontaneously Hypertensive Rats From Hypertension and Cardiorenal Dysfunctions Exacerbated by Dietary High-Salt Intake. Frontiers in Pharmacology. 2021; 12: 709467. https://doi.org/10.3389/fphar.2021.709467.

[48] Sato T, Sato C, Kadowaki A, Watanabe H, Ho L, Ishida J, *et al*. ELABELA-APJ axis protects from pressure overload heart failure and angiotensin II-induced cardiac damage. Cardiovascular Research. 2017; 113: 760–769. https://doi.org/10.1093/cvr/cvx061.

[49] Schreiber CA, Holditch SJ, Generous A, Ikeda Y. Sustained ELABELA Gene Therapy in High-salt Diet-induced Hypertensive Rats. Current Gene Therapy. 2017; 16: 349–360. https://doi.org/10.2174/1566523217666161121111906.

[50] Zhou S, Meng Z, Lu L, Xie J, Li L, Cheng H, *et al*. ELABELA-32 Alleviates Doxorubicin-Induced Chronic Cardiotoxicity by Inhibiting the TGF-β/Smad Signaling Pathway. Cardiovascular Toxicology. 2025; 25: 1009–1021. https://doi.org/10.1007/s12012-025-10010-w.

[51] Eberlé D, Marousez L, Hanssens S, Knauf C, Breton C, Deruelle P, *et al*. Elabela and Apelin actions in healthy and pathological pregnancies. Cytokine & Growth Factor Reviews. 2019; 46: 45–53. https://doi.org/10.1016/j.cytogfr.2019.03.003.

[52] Wang L, Wang X, He N, Yang L, Zou Y, Weng Z, *et al*. ELABELA targets the MEK/ERK axis to enhance trophoblast invasion in early-onset preeclampsia. Scientific Reports. 2025; 15: 29357. https://doi.org/10.1038/s41598-025-15533-4.

[53] Xu C. The Elabela in hypertension, cardiovascular disease, renal disease, and preeclampsia: an update. Journal of Hypertension. 2021; 39: 12–22. https://doi.org/10.1097/HJH.0000000000002591.

[54] Ho L, van Dijk M, Chye STJ, Messerschmidt DM, Chng SC, Ong S, *et al*. ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science. 2017; 357: 707–713. https://doi.org/10.1126/science.aam6607.

[55] Khan H, Uraneb S, Mushtaq R, Bano F. Effect of serum apelin and elabela levels in pregnancies complicated with preeclampsia in association to BMI, CRP and parity. Pakistan Journal of Pharmaceutical Sciences. 2023; 36: 749–753.

[56] Deniz R, Baykus Y, Ustebay S, Ugur K, Yavuzkir Ş, Aydin S. Evaluation of elabela, apelin and nitric oxide findings in maternal blood of normal pregnant women, pregnant women with pre-eclampsia, severe pre-eclampsia and umbilical arteries and venules of newborns. Journal of Obstetrics and Gynaecology. 2019; 39: 907–912. https://doi.org/10.1080/01443615.2019.1572727.

[57] Panaitescu B, Romero R, Gomez-Lopez N, Pacora P, Erez O, Vadillo-Ortega F, *et al*. ELABELA plasma concentrations are increased in women with late-onset preeclampsia. The Journal of Maternal-fetal & Neonatal Medicine: the Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2020; 33: 5–15. https://doi.org/10.1080/14767058.2018.1484089.

[58] Liu D, Luo D, Ge H, Zhang C, Wei S, Liang D, *et al*. Exposure to higher concentrations of exogenous ELABELA causes HTR-8/SVneo trophoblast cell dysfunction: A possible pathogenesis of pre-eclampsia. Pregnancy Hypertension. 2022; 30: 181–188. https://doi.org/10.1016/j.preghy.2022.10.005.

[59] Ma J, Hu H, Lin M, Chen L, Liu M, Li H, *et al*. ELABELA alleviates syncytiotrophoblast hypoxia/reoxygenation injury and preeclampsia-like symptoms in mice by reducing apoptosis. Placenta. 2021; 106: 30–39. https://doi.org/10.1016/j.placenta.2021.02.002.

[60] Zhou L, Sun H, Cheng R, Fan X, Lai S, Deng C. ELABELA, as a potential diagnostic biomarker of preeclampsia, regulates abnormally shallow placentation via APJ. American Journal of Physiology. Endocrinology and Metabolism. 2019; 316: E773–E781. https://doi.org/10.1152/ajpendo.00383.2018.