
REFERENCES:

1. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *The Journal of Clinical Endocrinology & Metabolism*. 2007;92(2):399-404.
2. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action. American College of Cardiology Foundation Washington DC; 2020.
3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *Journal of the American College of Cardiology*. 2020;76(25):2982-3021.
4. Jose AP, Prabhakaran D. World Hypertension Day: Contemporary issues faced in India. *The Indian journal of medical research*. 2019;149(5):567.
5. Hess PL, Al-Khalidi HR, Friedman DJ, Mulder H, Kucharska-Newton A, Rosamond WR, et al. The metabolic syndrome and risk of sudden cardiac death: the atherosclerosis risk in communities study. *Journal of the American Heart Association*. 2017;6(8):e006103.
6. Mazloomzadeh S, Zarandi FK, Shoghli A, Dinmohammadi H. Metabolic syndrome, its components and mortality: A population-based study. *Medical journal of the Islamic Republic of Iran*. 2019;33:11.
7. Collaborators GRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392(10159):1923.
8. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: trends in prevalence, incidence, and control. *Annual review of public health*. 2006;27:465-90.
9. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75(6):1334-57.
10. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. *Indian journal of endocrinology and metabolism*. 2011;15(Suppl4):S281.
11. L. Izzo J. Sympathoadrenal activity, catecholamines, and the pathogenesis of vasculopathic hypertensive target-organ damage. *American journal of hypertension*. 1989;2(12_Pt_2):305S-12S.
12. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. *Indian journal of endocrinology and metabolism*. 2011;15 Suppl 4(Suppl4):S281-8.

13. Rupp H, Jäger B. The renin-angiotensin system and the sympathetic nervous system in hypertension and congestive heart failure: implications for therapeutic interventions. *Journal of Clinical and Basic Cardiology*. 2001;4(1):47-51.
14. Du Y, Qiu J, Nelson SH, Wang DH. Regulation of type 1 ANG II receptor in vascular tissue: role of alpha1-adrenoreceptor. *Am J Physiol*. 1997;273(4 Pt 2):R1224-9.
15. Li HT, Long CS, Gray MO, Rokosh DG, Honbo NY, Karliner JS. Cross talk between angiotensin AT1 and alpha 1-adrenergic receptors: angiotensin II downregulates alpha 1a-adrenergic receptor subtype mRNA and density in neonatal rat cardiac myocytes. *Circ Res*. 1997;81(3):396-403.
16. Sumners C, Phillips M. Central injection of angiotensin II alters catecholamine activity in rat brain. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 1983;244(2):R257-R63.
17. Stadler T, Veltmar A, Qadri F, Unger T. Angiotensin II evokes noradrenaline release from the paraventricular nucleus in conscious rats. *Brain research*. 1992;569(1):117-22.
18. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. *J Am Soc Nephrol*. 1999;10 Suppl 12:S258-65.
19. Wolff DW, Buckalew VM, Jr., Strandhoy JW. Renal alpha 1- and alpha 2-adrenoceptor mediated vasoconstriction in dogs: comparison of phenylephrine, clonidine, and guanabenz. *J Cardiovasc Pharmacol*. 1984;6 Suppl 5:S793-8.
20. Zimmerman BG, Sybertz EJ, Wong PC. Interaction between sympathetic and renin-angiotensin system. *J Hypertens*. 1984;2(6):581-7.
21. Reid IA. Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. *Am J Physiol*. 1992;262(6 Pt 1):E763-78.
22. Starke K. Regulation of noradrenaline release by presynaptic receptor systems. *Rev Physiol Biochem Pharmacol*. 1977;77:1-124.
23. Rantala A, Kauma H, Lilja M, Savolainen M, Reunanen A, Kesäniemi Y. Prevalence of the metabolic syndrome in drug-treated hypertensive patients and control subjects. *Journal of internal medicine*. 1999;245(2):163-74.
24. Srivastava AK. Challenges in the treatment of cardiometabolic syndrome. *Indian Journal of Pharmacology*. 2012;44(2):155.
25. Ke C, Zhu X, Zhang Y, Shen Y. Metabolomic characterization of hypertension and dyslipidemia. *Metabolomics*. 2018;14(9):1-11.

-
26. Das UN. Renin–angiotensin–aldosterone system in insulin resistance and metabolic syndrome. *Journal of translational internal medicine*. 2016;4(2):66-72.
 27. Kishi T, Hirooka Y. Sympathoexcitation associated with Renin-Angiotensin system in metabolic syndrome. *International Journal of Hypertension*. 2013;2013.
 28. Huggett RJ, Burns J, Mackintosh AF, Mary DA. Sympathetic neural activation in nondiabetic metabolic syndrome and its further augmentation by hypertension. *Hypertension*. 2004;44(6):847-52.
 29. Esler M, Straznicky N, Eikelis N, Masuo K, Lambert G, Lambert E. Mechanisms of sympathetic activation in obesity-related hypertension. *Hypertension*. 2006;48(5):787-96.
 30. Salvetti A, Brogi G, Di Legge V, Bernini G. The inter-relationship between insulin resistance and hypertension. *Drugs*. 1993;46(2):149-59.
 31. Zhou M-S, Schulman IH, Zeng Q. Link between the renin–angiotensin system and insulin resistance: Implications for cardiovascular disease. *Vascular medicine*. 2012;17(5):330-41.
 32. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovascular diabetology*. 2018;17(1):1-14.
 33. Poulter NR, Borghi C, Parati G, Pathak A, Toli D, Williams B, et al. Medication adherence in hypertension. *Journal of hypertension*. 2020;38(4):579-87.
 34. Oparil S, Calhoun DA. Managing the patient with hard-to-control hypertension. *American family physician*. 1998;57(5):1007.
 35. Tikkanen I, Tikkanen T, Cao Z, Allen TJ, Davis BJ, Lassila M, et al. Combined inhibition of neutral endopeptidase with angiotensin converting enzyme or endothelin converting enzyme in experimental diabetes. *Journal of hypertension*. 2002;20(4):707-14.
 36. Battistini B, Daull P, Jeng AY. CGS 35601, a triple inhibitor of angiotensin converting enzyme, neutral endopeptidase and endothelin converting enzyme. *Cardiovascular drug reviews*. 2005;23(4):317-30.
 37. Murugesan N, Gu Z, Fadnis L, Tellew JE, Baska RAF, Yang Y, et al. Dual angiotensin II and endothelin A receptor antagonists: synthesis of 2 ‘-substituted N-3-isoxazolyl biphenylsulfonamides with improved potency and pharmacokinetics. *Journal of medicinal chemistry*. 2005;48(1):171-9.
 38. Palaniswamy C, Selvaraj DR, Palaniappan D. Dual angiotensin II and endothelin receptor antagonists. *American Journal of Therapeutics*. 2011;18(3):e67-e70.

-
39. Ramsay RR, Popovic-Nikolic MR, Nikolic K, Uliassi E, Bolognesi ML. A perspective on multi-target drug discovery and design for complex diseases. *Clinical and translational medicine*. 2018;7(1):3.
 40. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nature chemical biology*. 2008;4(11):682-90.
 41. Ramsay RR, Popovic-Nikolic MR, Nikolic K, Uliassi E, Bolognesi ML. A perspective on multi-target drug discovery and design for complex diseases. *Clinical and translational medicine*. 2018;7(1):1-14.
 42. Bottegoni G, Favia AD, Recanatini M, Cavalli A. The role of fragment-based and computational methods in polypharmacology. *Drug discovery today*. 2012;17(1-2):23-34.
 43. Lakka H-M, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *Jama*. 2002;288(21):2709-16.
 44. Meigs JB, Wilson PW, Nathan DM, D'Agostino RB, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes*. 2003;52(8):2160-7.
 45. Malone P, Agutter P. The aetiology of deep venous thrombosis. *Journal of the Association of Physicians*. 2006;99(9):581-93.
 46. Russo I. The prothrombotic tendency in metabolic syndrome: focus on the potential mechanisms involved in impaired haemostasis and fibrinolytic balance. *Scientifica*. 2012;2012.
 47. Ozkul A, Turgut ET, Akyol A, Yenisey C, Kadikoylu G, Tataroglu C, et al. The relationship between insulin resistance and hypercoagulability in acute ischemic stroke. *European neurology*. 2010;64(4):201-6.
 48. Mao X, Ait-Aissa K, Lagrange J, Youcef G, Louis H. Hypertension, hypercoagulability and the metabolic syndrome: A cluster of risk factors for cardiovascular disease. *Bio-medical materials and engineering*. 2012;22(1-3):35-48.
 49. Stewart LK, Kline JA. Metabolic syndrome increases risk of venous thromboembolism recurrence after acute deep vein thrombosis. *Blood advances*. 2020;4(1):127-35.
 50. Lee A. The role of rheological and haemostatic factors in hypertension. *Journal of human hypertension*. 1997;11(12):767-76.
 51. Vayá A, Mira Y, Ferrando F, Contreras M, Estelles A, España F, et al. Hyperlipidaemia and venous thromboembolism in patients lacking thrombophilic risk factors. *British journal of haematology*. 2002;118(1):255-9.

-
52. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation*. 2005;112(6):893-9.
 53. Sevinsky JR, Rao L, Ruf W. Ligand-induced protease receptor translocation into caveolae: a mechanism for regulating cell surface proteolysis of the tissue factor-dependent coagulation pathway. *The Journal of cell biology*. 1996;133(2):293-304.
 54. Chen Y-J, Lin-Chao S, Huang T-S, Yang M-L, Lu F-J. Humic acid induced growth retardation in a Sertoli cell line, TM4. *Life sciences*. 2001;69(11):1269-84.
 55. Gallus A, Lee L, Coghlan D. New aspects of the blood coagulation cascade, anticoagulants and vein thrombosis in Asia. *Annals of the Academy of Medicine, Singapore*. 2002;31(6):685-96.
 56. Kaur N, Pandey A, Shafiq N, Gupta A, Das R, Singh H, et al. Genetic and nongenetic determinants of variable warfarin dose requirements: a report from North India. *Public Health Genomics*. 2022;25(1-2):52-60.
 57. Stein P, Grandison D, Hua T, Slettehaugh P, Henry J, Turlapaty P, et al. Therapeutic level of oral anticoagulation with warfarin in patients with mechanical prosthetic heart valves: review of literature and recommendations based on international normalized ratio. *Postgraduate medical journal*. 1994;70:S72-S83.
 58. Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: a review of the pharmacology, dosing, and complications. *Current emergency and hospital medicine reports*. 2013;1(2):83-97.
 59. Blossom DB, Kallen AJ, Patel PR, Elward A, Robinson L, Gao G, et al. Outbreak of adverse reactions associated with contaminated heparin. *New England Journal of Medicine*. 2008;359(25):2674-84.
 60. Spinler SA, Willey VJ. A patient's guide to taking dabigatran etexilate. *Circulation*. 2011;124(8):e209-e11.
 61. Borensztajn K, Spek CA. Blood coagulation factor Xa as an emerging drug target. *Expert opinion on therapeutic targets*. 2011;15(3):341-9.
 62. Eriksson BI, Quinlan DJ, Weitz JJ. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clinical pharmacokinetics*. 2009;48(1):1-22.

-
63. Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. *Clinical pharmacokinetics*. 2013;52(4):243-54.
 64. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. *Thrombosis and haemostasis*. 2010;103(03):572-85.
 65. Cornier M-A, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. *Endocrine reviews*. 2008;29(7):777-822.
 66. Saklayen M. The Global Epidemic of the Metabolic Syndrome., 2018. *Current Hypertension Reports*.20(2):12.
 67. Abd El-Wahab EW, Shatat HZ, Charl F. Adapting a prediction rule for metabolic syndrome risk assessment suitable for developing countries. *Journal of primary care & community health*. 2019;10:2150132719882760.
 68. Tenenbaum A, Motro M, Schwammenthal E, Fisman EZ. Macrovascular complications of metabolic syndrome: an early intervention is imperative. *International journal of cardiology*. 2004;97(2):167-72.
 69. Kelli HM, Kassas I, Lattouf OM. Cardio metabolic syndrome: a global epidemic. *J Diabetes Metab*. 2015;6(3):2-14.
 70. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic medicine*. 1998;15(7):539-53.
 71. Huang PL. A comprehensive definition for metabolic syndrome. *Disease models & mechanisms*. 2009;2(5-6):231-7.
 72. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. *Current hypertension reports*. 2013;15(1):59-70.
 73. Unger RH. Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology*. 2003;144(12):5159-65.
 74. Akintunde AA, Ayodele OE, Akinwusi PO, Opadijo GO. Metabolic syndrome: comparison of occurrence using three definitions in hypertensive patients. *Clinical Medicine & Research*. 2011;9(1):26-31.
 75. Bøg-Hansen E, Lindblad U, Gullberg B, Melander A, Råstam L. Metabolic disorders associated with uncontrolled hypertension: Skaraborg hypertension and diabetes project. *Diabetes, Obesity and Metabolism*. 2003;5(6):379-87.

-
76. Mule G, Cottone S, Nardi E, Andronico G, Cerasola G. Metabolic syndrome in subjects with essential hypertension: relationships with subclinical cardiovascular and renal damage. *Minerva cardioangiologica*. 2006;54(2):173-94.
 77. Salvi P. Pulse waves. How vascular hemodynamics affects Blood pressure. 2012.
 78. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's heart disease: a textbook of cardiovascular medicine. 2011.
 79. Dzau VJ. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. *Circulation*. 1988;77(6 Pt 2):I4-13.
 80. Lee MA, Böhm M, Paul M, Ganten D. Tissue renin-angiotensin systems. Their role in cardiovascular disease. *Circulation*. 1993;87(5 Suppl):IV7-13.
 81. Vaneckova I, Maletinska L, Behuliak M, Nagelová V, Zicha J, Kunes J. Obesity-related hypertension: possible pathophysiological mechanisms. *J endocrinol*. 2014;223(3):R63-78.
 82. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *American Journal of Physiology-Cell Physiology*. 2007;292(1):C82-C97.
 83. Gopal F, Deshmukh A, Shah S, Mehta JL. Triad of metabolic syndrome, chronic kidney disease, and coronary heart disease with a focus on microalbuminuria: death by overeating. *Journal of the American College of Cardiology*. 2011;57(23):2303-8.
 84. Dai Y, Mercanti F, Dai D, Wang X, Ding Z, Pothineni NV, et al. LOX-1, a bridge between GLP-1R and mitochondrial ROS generation in human vascular smooth muscle cells. *Biochemical and Biophysical Research Communications*. 2013;437(1):62-6.
 85. Hageman WE, Buckley JP. Action of angiotensin II upon renal vascular resistance. *Journal of Pharmaceutical Sciences*. 1967;56(7):876-81.
 86. Rosivall L. Intrarenal renin–angiotensin system. *Molecular and cellular endocrinology*. 2009;302(2):185-92.
 87. Muniyappa R, Yavuz S. Metabolic actions of angiotensin II and insulin: a microvascular endothelial balancing act. *Molecular and cellular endocrinology*. 2013;378(1-2):59-69.
 88. Qi Y, Li H, Shenoy V, Li Q, Wong F, Zhang L, et al. Moderate cardiac-selective overexpression of angiotensin II type 2 receptor protects cardiac functions from ischaemic injury. *Experimental physiology*. 2012;97(1):89-101.

-
89. Mukoyama M, Nakajima M, Horiuchi M, Sasamura H, Pratt RE, Dzau V. Expression cloning of type 2 angiotensin II receptor reveals a unique class of seven-transmembrane receptors. *Journal of Biological Chemistry*. 1993;268(33):24539-42.
 90. Royea J, Hamel E. Brain angiotensin II and angiotensin IV receptors as potential Alzheimer's disease therapeutic targets. *GeroScience*. 2020;42(5):1237-56.
 91. Yamano Y, Ohyama K, Chaki S, Guo DF, Inagami T. Identification of amino acid residues of rat angiotensin II receptor for ligand binding by site directed mutagenesis. *Biochem Biophys Res Commun*. 1992;187(3):1426-31.
 92. Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. *Clinical science*. 2007;112(8):417-28.
 93. Dinh DT, Frauman AG, Johnston CI, FABIANI ME. Angiotensin receptors: distribution, signalling and function. *Clinical science*. 2001;100(5):481-92.
 94. Griendling KK, Ushio-Fukai M, Lassègue B, Alexander RW. Angiotensin II signaling in vascular smooth muscle: new concepts. *Hypertension*. 1997;29(1):366-70.
 95. Nickenig G, Röling Jr, Strehlow K, Schnabel P, Böhm M. Insulin induces upregulation of vascular AT1 receptor gene expression by posttranscriptional mechanisms. *Circulation*. 1998;98(22):2453-60.
 96. Liu H-W, Iwai M, Takeda-Matsubara Y, Wu L, Li J-M, Okumura M, et al. Effect of estrogen and AT1 receptor blocker on neointima formation. *Hypertension*. 2002;40(4):451-7.
 97. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. *Pharmacological reviews*. 2000;52(4):639-72.
 98. Touyz RM, Schiffrin EL. Ang II-stimulated superoxide production is mediated via phospholipase D in human vascular smooth muscle cells. *Hypertension*. 1999;34(4):976-82.
 99. Kusuhara M, Takahashi E, Peterson TE, Abe J-i, Ishida M, Han J, et al. p38 Kinase is a negative regulator of angiotensin II signal transduction in vascular smooth muscle cells: effects on Na⁺/H⁺ exchange and ERK1/2. *Circulation research*. 1998;83(8):824-31.
 100. Griendling KK, Ushio-Fukai M. Reactive oxygen species as mediators of angiotensin II signaling. *Regulatory peptides*. 2000;91(1-3):21-7.
 101. Mancina G, Grassi G. The autonomic nervous system and hypertension. *Circulation research*. 2014;114(11):1804-14.

-
102. Joyner MJ, Charkoudian N, Wallin BG. A sympathetic view of the sympathetic nervous system and human blood pressure regulation. *Experimental physiology*. 2008;93(6):715-24.
 103. Wallin BG, Charkoudian N. Sympathetic neural control of integrated cardiovascular function: insights from measurement of human sympathetic nerve activity. *Muscle & nerve*. 2007;36(5):595-614.
 104. Seravalle G, Grassi G. Sympathetic nervous system and hypertension: New evidences. *Autonomic Neuroscience*. 2022:102954.
 105. Julius S, Randall OS, Esler MD, Kashima T, Ellis C, Bennett J. Altered cardiac responsiveness and regulation in the normal cardiac output type of borderland hypertension. *Circulation Research*. 1975;36(6):199-207.
 106. Grassi G, Seravalle G, Stella ML, Mancia G. Pathophysiological aspects of hypertensive disease in women. *Journal of hypertension Supplement: Official Journal of the International Society of Hypertension*. 2002;20(2):S6-10.
 107. Narkiewicz K, Phillips BG, Kato M, Hering D, Bieniaszewski L, Somers VK. Gender-selective interaction between aging, blood pressure, and sympathetic nerve activity. *Hypertension*. 2005;45(4):522-5.
 108. Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. *Current hypertension reports*. 2009;11(3):199-205.
 109. Grassi G, Seravalle G, Dell'Oro R, Turri C, Bolla GB, Mancia G. Adrenergic and reflex abnormalities in obesity-related hypertension. *hypertension*. 2000;36(4):538-42.
 110. Grassi G, Dell'Oro R, Quarti-Trevano F, Scopelliti F, Seravalle G, Paleari F, et al. Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. *Diabetologia*. 2005;48(7):1359-65.
 111. Du Y, Qiu J, Nelson SH, Wang DH. Regulation of type 1 Ang II receptor in vascular tissue: role of $\alpha 1$ -adrenoreceptor. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 1997;273(4):R1224-R9.
 112. Reid AC, Mackins CJ, Seyedi N, Levi R, Silver RB. Coupling of angiotensin II AT1 receptors to neuronal NHE activity and carrier-mediated norepinephrine release in myocardial ischemia. *American Journal of Physiology-Heart and Circulatory Physiology*. 2004;286(4):H1448-H54.
 113. Jerez S, Sierra L, Scacchi F, de Bruno MP. Hypercholesterolemia modifies angiotensin II desensitisation and cross talk between $\alpha 1$ -adrenoceptor and angiotensin AT1 receptor in rabbit aorta. *European journal of pharmacology*. 2010;635(1-3):149-55.

-
114. Vittorio TJ, Fudim M, Wagman G, Kosmas CE. Alpha-1 adrenoceptor–angiotensin II type 1 receptor cross-talk and its relevance in clinical medicine. *Cardiology in Review*. 2014;22(2):51-5.
 115. Van Zwieten P, De Jonge A. Interaction between the adrenergic and renin-angiotensin-aldosterone-systems. *Postgraduate medical journal*. 1986;62:23-7.
 116. Lang CC, Rahman AR, Balfour D, Struthers AD. Prazosin blunts the antinatriuretic effect of circulating angiotensin II in man. *Journal of hypertension*. 1992;10(11):1387-95.
 117. Farivar RS, Crawford DC, Chobanian AV, Brecher P. Effect of angiotensin II blockade on the fibroproliferative response to phenylephrine in the rat heart. *Hypertension*. 1995;25(4):809-13.
 118. Li H-T, Long CS, Gray MO, Rokosh DG, Honbo NY, Karliner JS. Cross talk between angiotensin AT1 and α 1-adrenergic receptors: angiotensin II downregulates α 1a-adrenergic receptor subtype mRNA and density in neonatal rat cardiac myocytes. *Circulation research*. 1997;81(3):396-403.
 119. Barrett-O’Keefe Z, Witman MA, McDaniel J, Fjeldstad AS, Trinity JD, Ives SJ, et al. Angiotensin II potentiates α -adrenergic vasoconstriction in the elderly. *Clinical Science*. 2013;124(6):413-22.
 120. Youngren J. Regulation of insulin receptor function. *Cellular and Molecular Life Sciences*. 2007;64(7):873-91.
 121. Inoue G, Cheatham B, Emkey R, Kahn CR. Dynamics of insulin signaling in 3T3-L1 adipocytes: differential compartmentalization and trafficking of insulin receptor substrate (IRS)-1 and IRS-2. *Journal of Biological Chemistry*. 1998;273(19):11548-55.
 122. Taguchi A, White MF. Insulin-like signaling, nutrient homeostasis, and life span. *Annu Rev Physiol*. 2008;70:191-212.
 123. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren J-M, Previs S, et al. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*. 1998;391(6670):900-4.
 124. Giraud J, Leshan R, Lee Y-H, White MF. Nutrient-dependent and insulin-stimulated phosphorylation of insulin receptor substrate-1 on serine 302 correlates with increased insulin signaling. *Journal of Biological Chemistry*. 2004;279(5):3447-54.
 125. Andreozzi F, Laratta E, Sciacqua A, Perticone F, Sesti G. Angiotensin II impairs the insulin signaling pathway promoting production of nitric oxide by inducing phosphorylation of insulin receptor substrate-1 on Ser312 and Ser616 in human umbilical vein endothelial cells. *Circulation research*. 2004;94(9):1211-8.

-
126. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-80.
 127. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *The Journal of clinical investigation*. 2007;117(1):175-84.
 128. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *The Journal of clinical investigation*. 2011;121(6):2094-101.
 129. Engeli S, Negrel R, Sharma AM. Physiology and pathophysiology of the adipose tissue renin-angiotensin system. *Hypertension*. 2000;35(6):1270-7.
 130. Sharma AM, Janke Jr, Gorzelniak K, Engeli S, Luft FC. Angiotensin blockade prevents type 2 diabetes by formation of fat cells. *Hypertension*. 2002;40(5):609-11.
 131. Lee MH, Song HK, Ko GJ, Kang YS, Han SY, Han KH, et al. Angiotensin receptor blockers improve insulin resistance in type 2 diabetic rats by modulating adipose tissue. *Kidney international*. 2008;74(7):890-900.
 132. Jin H-M, Pan Y. Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. *Nephrology Dialysis Transplantation*. 2007;22(7):1943-9.
 133. Grassi G, Seravalle G, Dell'Oro R, Trevano FQ, Bombelli M, Scopelliti F, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. *Journal of hypertension*. 2003;21(9):1761-9.
 134. Landsberg L, Krieger DR. Obesity, metabolism, and the sympathetic nervous system. *American journal of hypertension*. 1989;2(3_Pt_2):125S-32S.
 135. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, et al. Sympathetic activation in obese normotensive subjects. *Hypertension*. 1995;25(4):560-3.
 136. Hall J, Brands M, Hildebrandt D, Kuo J, Fitzgerald S. Role of sympathetic nervous system and neuropeptides in obesity hypertension. *Brazilian Journal of Medical and Biological Research*. 2000;33:605-18.
 137. Kassab S, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP. Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension*. 1995;25(4):893-7.
 138. de Graaf JC, Banga JD, Moncada S, Palmer RM, de Groot PG, Sixma JJ. Nitric oxide functions as an inhibitor of platelet adhesion under flow conditions. *Circulation*. 1992;85(6):2284-90.

-
139. Konukoglu D, Uzun H. Endothelial Dysfunction and Hypertension. *Advances in experimental medicine and biology*. 2017;956:511-40.
 140. Landa-Galvan HV, Rios-Castro E. Metabolic syndrome diminishes insulin-induced Akt activation and causes a redistribution of Akt-interacting proteins in cardiomyocytes. 2020;15(1):e0228115.
 141. Wilson C, Zhang X, Buckley C, Heathcote HR, Lee MD, McCarron JG. Increased vascular contractility in hypertension results from impaired endothelial calcium signaling. *Hypertension*. 2019;74(5):1200-14.
 142. Ziegler MG, Mills P, Dimsdale JE. Hypertensives' pressor response to norepinephrine: analysis by infusion rate and plasma levels. *American journal of hypertension*. 1991;4(7_Pt_1):586-91.
 143. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Annals of internal medicine*. 2003;139(9):761-76.
 144. Calhoun DA, Mutinga ML, Collins AS, Wyss JM, Oparil S. Normotensive blacks have heightened sympathetic response to cold pressor test. *Hypertension*. 1993;22(6):801-5.
 145. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37(12):1595-607.
 146. Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. *The Journal of clinical endocrinology and metabolism*. 2003;88(6):2399-403.
 147. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Therapeutic advances in cardiovascular disease*. 2017;11(8):215-25.
 148. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *Journal of the American College of Cardiology*. 2010;56(14):1113-32.
 149. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735-52.
 150. Morphy R, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. *Drug discovery today*. 2004;9(15):641-51.

-
151. Morphy R, Rankovic Z. Designed multiple ligands. An emerging drug discovery paradigm. *Journal of medicinal chemistry*. 2005;48(21):6523-43.
 152. de Cates AN, Farr MR, Wright N, Jarvis MC, Rees K, Ebrahim S, et al. Fixed-dose combination therapy for the prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews*. 2014(4).
 153. Gautam CS, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. *British journal of clinical pharmacology*. 2008;65(5):795.
 154. Hall SE, Mao A, Nicolaidou V, Finelli M, Wise EL, Nedjai B, et al. Elucidation of binding sites of dual antagonists in the human chemokine receptors CCR2 and CCR5. *Molecular pharmacology*. 2009;75(6):1325-36.
 155. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883-99.
 156. Tao L, Zhu F, Xu F, Chen Z, Jiang YY, Chen YZ. Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs. *Pharmacological research*. 2015;102:123-31.
 157. Zhang J, Liu X, Xie XB, Cheng XC, Wang RL. Multitargeted bioactive ligands for PPAR s discovered in the last decade. *Chemical Biology & Drug Design*. 2016;88(5):635-63.
 158. Trstenjak U, Kikelj D. Multitarget cardiovascular drugs. *Current Medicinal Chemistry*. 2011;18(17):2531-42.
 159. Turnaturi R, Arico G, Ronsisvalle G, Parenti C, Pasquinucci L. Multitarget opioid ligands in pain relief: New players in an old game. *European Journal of Medicinal Chemistry*. 2016;108:211-28.
 160. Amin A, Attur M, Pillinger M, Abramson S. The pleiotropic functions of aspirin: mechanisms of action. *Cellular and Molecular Life Sciences CMLS*. 1999;56(3):305-12.
 161. Varjabedian L, Bourji M, Pourafkari L, Nader ND. Cardioprotection by metformin: beneficial effects beyond glucose reduction. *American Journal of Cardiovascular Drugs*. 2018;18(3):181-93.
 162. Rahn K. Clinical experience with dual-acting drugs in hypertension. *The clinical investigator*. 1992;70(2):S39-S42.
 163. Papademetriou V, Tsioufis C, Gradman A, Punzi H. Difficult-to-treat or resistant hypertension: etiology, pathophysiology, and innovative therapies. *Hindawi*; 2011.
 164. Guerrero-García C, Rubio-Guerra AF. Combination therapy in the treatment of hypertension. *Drugs in context*. 2018;7.

-
165. Ma H, Huang B, Zhang Y. Recent advances in multitarget-directed ligands targeting G-protein-coupled receptors. *Drug discovery today*. 2020;25(9):1682-92.
166. Morphy R, Rankovic Z. Fragments, network biology and designing multiple ligands. *Drug discovery today*. 2007;12(3-4):156-60.
167. Costantino L, Barlocco D. Designed multiple ligands: basic research vs clinical outcomes. *Current medicinal chemistry*. 2012;19(20):3353-87.
168. Hopkins AL, Mason JS, Overington JP. Can we rationally design promiscuous drugs? *Current opinion in structural biology*. 2006;16(1):127-36.
169. East SP, Silver LL. Multitarget ligands in antibacterial research: progress and opportunities. *Expert opinion on drug discovery*. 2013;8(2):143-56.
170. Leonetti G, Egan CG. Use of carvedilol in hypertension: an update. *Vascular health and risk management*. 2012;8:307.
171. Katholi RE, Couri DM. Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications. *International journal of hypertension*. 2011;2011.
172. Kimoto S, Haruna M, Matsuura E, Uno O, Ishii M, Hirono S, et al. Pharmacological studies on a new antihypertensive agent, S-2150, a benzothiazepine derivative: 3. Hypotensive and antimyocardial-stunning effects in dogs. *Journal of cardiovascular pharmacology*. 1997;29(2):180-7.
173. Kowala MC, Murugesan N, Tellet J, Carlson K, Monshizadegan H, Ryan C, et al. Novel dual action AT1 and ETA receptor antagonists reduce blood pressure in experimental hypertension. *Journal of Pharmacology and Experimental Therapeutics*. 2004;309(1):275-84.
174. Imayama I, Ichiki T, Inanaga K, Ohtsubo H, Fukuyama K, Ono H, et al. Telmisartan downregulates angiotensin II type 1 receptor through activation of peroxisome proliferator-activated receptor γ . *Cardiovascular research*. 2006;72(1):184-90.
175. Kajiya T, Ho C, Wang J, Vilardi R, Kurtz TW. Molecular and cellular effects of azilsartan: a new generation angiotensin II receptor blocker. *Journal of hypertension*. 2011;29(12):2476-83.
176. Hadizadeh F, IMEN SM, Esmaeili P, Taghiabadi M. Synthesis and effects of novel dihydropyridines as dual calcium channel blocker and angiotensin antagonist on isolated rat aorta. 2010.

-
177. Wang Y, Landheer S, van Gilst WH, van Amerongen A, Hammes H-P, Henning RH, et al. Attenuation of renovascular damage in Zucker diabetic fatty rat by NWT-03, an egg protein hydrolysate with ACE-and DPP4-inhibitory Activity. 2012.
 178. Odori S, Hosoda K, Tomita T, Fujikura J, Kusakabe T, Kawaguchi Y, et al. GPR119 expression in normal human tissues and islet cell tumors: evidence for its islet-gastrointestinal distribution, expression in pancreatic beta and alpha cells, and involvement in islet function. *Metabolism*. 2013;62(1):70-8.
 179. Ritchie S, Connell J. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutrition, Metabolism and cardiovascular diseases*. 2007;17(4):319-26.
 180. Mertens I, Gaal LV. Obesity, haemostasis and the fibrinolytic system. *Obesity reviews*. 2002;3(2):85-101.
 181. Mina A, Favaloro EJ, Koutts J, editors. Hemostatic dysfunction associated with endocrine disorders as a major risk factor and cause of human morbidity and mortality: a comprehensive meta-review. *Seminars in thrombosis and hemostasis*; 2007: © Thieme Medical Publishers.
 182. Lazzaroni MG, Piantoni S, Masneri S, Garrafa E, Martini G, Tincani A, et al. Coagulation dysfunction in COVID-19: the interplay between inflammation, viral infection and the coagulation system. *Blood reviews*. 2021;46:100745.
 183. Eslamifar Z, Behzadifard M, Soleimani M, Behzadifard S. Coagulation abnormalities in SARS-CoV-2 infection: overexpression tissue factor. *Thrombosis journal*. 2020;18(1):1-4.
 184. Ziliotto N, Bernardi F, Jakimovski D, Zivadinov R. Coagulation pathways in neurological diseases: multiple sclerosis. *Frontiers in Neurology*. 2019;10:409.
 185. Habib A, Petrucci G, Rocca B. Pathophysiology of thrombosis in peripheral artery disease. *Current Vascular Pharmacology*. 2020;18(3):204-14.
 186. Grover SP, Mackman N. Intrinsic pathway of coagulation and thrombosis: Insights from animal models. *Arteriosclerosis, thrombosis, and vascular biology*. 2019;39(3):331-8.
 187. Panova-Noeva M, Eggebrecht L, Prochaska JH, Wild PS. Potential of multidimensional, large-scale biodatabases to elucidate coagulation and platelet pathways as an approach towards precision medicine in thrombotic disease. *Hämostaseologie*. 2019;39(02):152-63.
 188. Chaudhry R, Usama SM, Babiker HM. Physiology, coagulation pathways. 2018.
 189. Gailani D, Renné T. Intrinsic pathway of coagulation and arterial thrombosis. *Arteriosclerosis, thrombosis, and vascular biology*. 2007;27(12):2507-13.

-
190. Mackman N, Tilley RE, Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arteriosclerosis, thrombosis, and vascular biology*. 2007;27(8):1687-93.
 191. Mann K, Nesheim M, Church W, Haley P, Krishnaswamy S. Surface-dependent reactions of the vitamin K-dependent enzyme complexes. 1990.
 192. Stamatoyannopoulos G, Nienhuis AW, Leder P, Majerus P. The molecular basis of blood diseases. 1987.
 193. Borensztajn K, Peppelenbosch MP, Spek CA. Factor Xa: at the crossroads between coagulation and signaling in physiology and disease. *Trends in molecular medicine*. 2008;14(10):429-40.
 194. Zhou Q, Bea F, Preusch M, Wang H, Isermann B, Shahzad K, et al. Evaluation of plaque stability of advanced atherosclerotic lesions in apo E-deficient mice after treatment with the oral factor Xa inhibitor rivaroxaban. *Mediators of inflammation*. 2011;2011.
 195. Sevigny LM, Austin KM, Zhang P, Kasuda S, Koukos G, Sharifi S, et al. Protease-Activated Receptor-2 Modulates Protease-Activated Receptor-1–Driven Neointimal Hyperplasia. *Arteriosclerosis, thrombosis, and vascular biology*. 2011;31(12):e100-e6.
 196. Borissoff JJ, Heeneman S, Kiliç E, Kašák P, Van Oerle R, Winckers K, et al. Early atherosclerosis exhibits an enhanced procoagulant state. *Circulation*. 2010;122(8):821-30.
 197. Nierodzik ML, Karparkin S. Thrombin induces tumor growth, metastasis, and angiogenesis: Evidence for a thrombin-regulated dormant tumor phenotype. *Cancer cell*. 2006;10(5):355-62.
 198. Shinagawa K, Martin JA, Ploplis VA, Castellino FJ. Coagulation factor Xa modulates airway remodeling in a murine model of asthma. *American journal of respiratory and critical care medicine*. 2007;175(2):136-43.
 199. Mann K, Brummel K, Butenas S. What is all that thrombin for? *Journal of Thrombosis and Haemostasis*. 2003;1(7):1504-14.
 200. Huisman M, Borris L, Dahl O, Eriksson B, Haas S, Kakkar A, et al. An oral, direct Factor Xa inhibitor, rivaroxaban: once-daily regimen for thromboprophylaxis after hip replacement. *Pathophysiol Haemost Thromb*. 2006;35:A1.
 201. Lassen M, Davidson B, Gallus A. On behalf of the apixaban investigators. A phase II randomized, double-blind, eight-arm, parallel-group, dose-response study of apixaban, a new oral Factor Xa inhibitor for the prevention of deep vein thrombosis in knee replacement surgery. *Blood*. 2006;108.

-
202. Hoffman M, Monroe III DM. A cell-based model of hemostasis. *Thrombosis and haemostasis*. 2001;85(06):958-65.
 203. Becker RC. Factor Xa-A pleuripotential protease. *Journal of thrombosis and thrombolysis*. 2003;15(1):5.
 204. Davie EW, Kulman JD, editors. An overview of the structure and function of thrombin. *Seminars in thrombosis and hemostasis*; 2006: Copyright© 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New
 205. Esmon CT. The protein C pathway. *Chest*. 2003;124(3):26S-32S.
 206. Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. *Journal of Thrombosis and Haemostasis*. 2005;3(8):1800-14.
 207. Petros S, Siegemund T, Siegemund A, Engelmann L. The effect of different anticoagulants on thrombin generation. *Blood coagulation & fibrinolysis*. 2006;17(2):131-7.
 208. Eriksson BI, Kålebo P, Bergqvist D, Dahl OE, Lindbratt S, Bylock A, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *The Lancet*. 2002;360(9344):1441-7.
 209. Davis EM, Packard KA, Knezevich JT, Campbell JA. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2011;31(10):975-1016.
 210. De Caterina R. The current role of anticoagulants in cardiovascular medicine. *Journal of Cardiovascular Medicine*. 2009;10(8):595-604.
 211. Kumbhani DJ, Cannon CP, Beavers CJ, Bhatt DL, Cuker A, Gluckman TJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology Solution Set Oversight Committee. *Journal of the American College of Cardiology*. 2021;77(5):629-58.
 212. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The role of anticoagulation in COVID-19-induced hypercoagulability. *Current cardiology reports*. 2020;22(7):1-6.
 213. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of

thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e531S-e75S.

214. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2008;133(6):160S-98S.

215. Bauer KA. New anticoagulants: anti IIa vs anti Xa—is one better? *Journal of thrombosis and thrombolysis*. 2006;21(1):67-72.

216. ARUNLAKSHANA Ot, Schild H. Some quantitative uses of drug antagonists. *British journal of pharmacology and chemotherapy*. 1959;14(1):48-58.

217. Iglarz M, Binkert C, Morrison K, Fischli W, Gatfield J, Treiber A, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *Journal of Pharmacology and Experimental Therapeutics*. 2008;327(3):736-45.

218. Parasuraman S, Raveendran R. Measurement of invasive blood pressure in rats. *Journal of pharmacology & pharmacotherapeutics*. 2012;3(2):172.

219. Ghasemi M, Turnbull T, Sebastian S, Kempson I. The MTT assay: utility, limitations, pitfalls, and interpretation in bulk and single-cell analysis. *International journal of molecular sciences*. 2021;22(23):12827.

220. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*. 2017;7(1):1-13.

221. Riyadi P, Sari I, Kurniasih R, Agustini T, Swastawati F, Herawati V, et al., editors. SwissADME predictions of pharmacokinetics and drug-likeness properties of small molecules present in spirulina platensis. *IOP Conference Series: Earth and Environmental Science*; 2021: IOP Publishing.

222. Pires DE, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of medicinal chemistry*. 2015;58(9):4066-72.

223. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Research*. 2021;49(W1):W5-W14.

224. O'Sullivan J, Finnie SL, Teenan O, Cairns C, Boyd A, Bailey MA, et al. Refining the Mouse Subtotal Nephrectomy in Male 129S2/SV Mice for Consistent Modeling of Progressive

- Kidney Disease With Renal Inflammation and Cardiac Dysfunction. *Frontiers in Physiology*. 2019;10(1365).
225. Soliman E, Behairy SF, El-maraghy NN, Elshazly SM. PPAR- γ agonist, pioglitazone, reduced oxidative and endoplasmic reticulum stress associated with L-NAME-induced hypertension in rats. *Life Sciences*. 2019;239:117047.
226. Vizioli EO, Spadin MD, Correa FM, Viaro F, Evora PR, Chies AB. Acetylcholine-induced aortic relaxation studied in salbutamol treated rats. *Journal of smooth muscle research* = *Nihon Heikatsukin Gakkai kikanshi*. 2005;41(5):271-81.
227. Trinder P. Estimation of blood glucose by GOD-POD method. *Ann Clin Bio Chem*. 1969;6:24.
228. Warnick GR, Wood PD. National Cholesterol Education Program recommendations for measurement of high-density lipoprotein cholesterol: executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clinical chemistry*. 1995;41(10):1427-33.
229. Stein A, Mayer G. Triglycerides: GPO-Pap, End point Assay. *Clin Chern*. 1995;41:1421-6.
230. Toro G, Ackermann PG. *Practical clinical chemistry*: Little Brown & Company; 1975.
231. Fossati P, Prencipe L, Berti G. Use of 3, 5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine. *Clinical chemistry*. 1980;26(2):227-31.
232. Schoenfeld R, Lewellan C. A colorimetric method for determination of serum chloride. *Clinical Chemistry*. 1964;10(6):533-9.
233. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *Journal of biological chemistry*. 1951;193:265-75.
234. Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. *Nitric oxide*. 2001;5(1):62-71.
235. Slater T, Sawyer B. The stimulatory effects of carbon tetrachloride and other halogenoalkanes on peroxidative reactions in rat liver fractions in vitro. General features of the systems used. *Biochemical Journal*. 1971;123(5):805-14.
236. Moron MS, Depierre JW, Mannervik B. Levels of glutathione, glutathione reductase and glutathione S-transferase activities in rat lung and liver. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 1979;582(1):67-78.

-
237. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. *Journal of Biological chemistry*. 1972;247(10):3170-5.
238. Aebi H. Catalase in vitro. *Methods in enzymology*. 1984;105:121-6.
239. Kishino E, Ito T, Fujita K, Kiuchi Y. A mixture of the *Salacia reticulata* (Kotala himbutu) aqueous extract and cyclodextrin reduces the accumulation of visceral fat mass in mice and rats with high-fat diet-induced obesity. *The Journal of nutrition*. 2006;136(2):433-9.
240. Iacobellis G, Petramala L, Cotesta D, Pergolini M, Zinamosca L, Cianci R, et al. Adipokines and cardiometabolic profile in primary hyperaldosteronism. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(5):2391-8.
241. Supriya R, Tam BT, Angus PY, Lee PH, Lai CW, Cheng KK, et al. Adipokines demonstrate the interacting influence of central obesity with other cardiometabolic risk factors of metabolic syndrome in Hong Kong Chinese adults. *PloS one*. 2018;13(8).
242. Zhao Y, Jiang M, Zhou S, Wu S, Zhang X, Ma L, et al. Design, synthesis and structure–activity relationship of oxazolidinone derivatives containing novel S4 ligand as FXa inhibitors. *European Journal of Medicinal Chemistry*. 2015;96:369-80.
243. Wang Y, Sun X, Yang D, Guo Z, Fan X, Nie M, et al. Design, synthesis, and structure–activity relationship of novel and effective apixaban derivatives as FXa inhibitors containing 1, 2, 4-triazole/pyrrole derivatives as P2 binding element. *Bioorganic & medicinal chemistry*. 2016;24(21):5646-61.
244. Co-operation OfE, Development. Test No. 425: acute oral toxicity: up-and-down procedure: OECD publishing; 2008.
245. Yu C, Qi D, Lian W, Li QZ, Li HJ, Fan HY. Effects of danshensu on platelet aggregation and thrombosis: in vivo arteriovenous shunt and venous thrombosis models in rats. *PLoS One*. 2014;9(11):e110124.
246. Chang KS, Stevens WC. Endothelium-dependent increase in vascular sensitivity to phenylephrine in long-term streptozotocin diabetic rat aorta. *British journal of pharmacology*. 1992;107(4):983-90.
247. Brailoiu E, Filipeanu CM, Tica A, Toma CP, De Zeeuw D, Nelemans SA. Contractile effects by intracellular angiotensin II via receptors with a distinct pharmacological profile in rat aorta. *British journal of pharmacology*. 1999;126(5):1133-8.
-

-
248. Testa R, Guarneri L, Poggesi E, Simonazzi I, Taddei C, Leonardi A. Mediation of noradrenaline-induced contractions of rat aorta by the α 1B-adrenoceptor subtype. *British journal of pharmacology*. 1995;114(4):745.
249. Yamamoto Y, Koike K. Characterization of α 1-adrenoceptor-mediated contraction in the mouse thoracic aorta. *European journal of pharmacology*. 2001;424(2):131-40.
250. Ott L, Weiner D, Cheng H, Woodward J. Estimating pA2 values for different designs. *Journal of Pharmacological Methods*. 1981;5(1):75-92.
251. Huang J, Huang Y, Zhu L, Yuan M, Huang L. Design, synthesis and α 1-adrenoreceptor blocking activity of new arylpiperazines containing acetophenone substituents. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 2014;69(8):578-84.
252. Corriu C, Bernard S, Schott C, Stoclet J-C. Effects of losartan on contractile responses of conductance and resistance arteries from rats. *Journal of cardiovascular pharmacology*. 1995;26(5):688-92.
253. le Tran Y, Forster C. Effect of angiotensin receptor blockade in the rabbit aorta: influence of the endothelium. *Canadian journal of physiology and pharmacology*. 1996;74(12):1277-86.
254. Merlos M, Rabasseda X, Silvestre J. Discovery of new angiotensin II receptor antagonists. A review of pharmacological studies. *Methods and findings in experimental and clinical pharmacology*. 1998;20(9):805.
255. Dale M, Haylett D. *Pharmacology Condensed*. 1st Edn. Chirchill Livingston. Elsevier Ltd., UK. pp; 2004.
256. Tallarida RJ, Cowan A, Adler MW. pA2 and receptor differentiation: a statistical analysis of competitive antagonism. *Life sciences*. 1979;25(8):637-54.
257. Agrawal N, Machhi J, Rathwa V, Kanhed AM, Patel S, Murumkar P, et al. Exploration of 6, 7-dimethoxyquinazoline derivatives as dual acting α 1-and AT 1-receptor antagonists: synthesis, evaluation, pharmacophore & 3D-QSAR modeling and receptor docking studies. *RSC advances*. 2016;6(36):30661-82.
258. Steppeler A, Tanaka T, Starke K. A comparison of pre-and postsynaptic α -adrenergic effects of phenylephrine and tramazoline on blood vessels of the rabbit in vivo. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 1978;304(3):223-30.
259. Rossoni LV, dos Santos L, Barker LA, Vassallo DV. Ouabain Changes Arterial Blood Pressure and Vascular Reactivity to Phenylephrine in l-NAME–Induced Hypertension. *Journal of cardiovascular pharmacology*. 2003;41(1):105-16.
-

-
260. Rosenbaugh EG, Roat JW, Gao L, Yang R-F, Manickam DS, Yin J-X, et al. The attenuation of central angiotensin II-dependent pressor response and intra-neuronal signaling by intracarotid injection of nanoformulated copper/zinc superoxide dismutase. *Biomaterials*. 2010;31(19):5218-26.
261. Liles JT, Dabisch PA, Hude KE, Pradhan L, Varner KJ, Porter JR, et al. Pressor responses to ephedrine are mediated by a direct mechanism in the rat. *Journal of Pharmacology and Experimental Therapeutics*. 2006;316(1):95-105.
262. Padia SH, Howell NL, Siragy HM, Carey RM. Renal angiotensin type 2 receptors mediate natriuresis via angiotensin III in the angiotensin II type 1 receptor-blocked rat. *Hypertension*. 2006;47(3):537-44.
263. Smith SA, Williams MA, Leal AK, Mitchell JH, Garry MG. Exercise pressor reflex function is altered in spontaneously hypertensive rats. *The Journal of physiology*. 2006;577(3):1009-20.
264. Oliverio MI, Best CF, Kim H, Arendshorst WJ, Smithies O, Coffman TM. Angiotensin II responses in AT1A receptor-deficient mice: a role for AT1B receptors in blood pressure regulation. *American Journal of Physiology-Renal Physiology*. 1997;272(4):F515-F20.
265. McKim J, James M. Building a tiered approach to in vitro predictive toxicity screening: a focus on assays with in vivo relevance. *Combinatorial chemistry & high throughput screening*. 2010;13(2):188-206.
266. Selick HE, Beresford AP, Tarbit MH. The emerging importance of predictive ADME simulation in drug discovery. *Drug Discovery Today*. 2002;7(2):109-16.
267. Gombar VK, Silver IS, Zhao Z. Role of ADME characteristics in drug discovery and their in silico evaluation: in silico screening of chemicals for their metabolic stability. *Current topics in medicinal chemistry*. 2003;3(11):1205-25.
268. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharmaceutica Sinica B*. 2022.
269. Wang J, Urban L. The impact of early ADME profiling on drug discovery and development strategy. *DDW Drug Discovery World*. 2004;5(4):73-86.
270. Wishart DS. Improving early drug discovery through ADME modelling. *Drugs in R & D*. 2007;8(6):349-62.
271. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews*. 1997;23(1-3):3-25.
-

-
272. Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *Journal of medicinal chemistry*. 2002;45(12):2615-23.
273. Chen X, Li H, Tian L, Li Q, Luo J, Zhang Y. Analysis of the physicochemical properties of acaricides based on Lipinski's rule of five. *Journal of computational biology*. 2020;27(9):1397-406.
274. Leeson PD, Young RJ. Molecular property design: does everyone get it? : ACS Publications; 2015. p. 722-5.
275. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. *Drug discovery today: Technologies*. 2004;1(4):337-41.
276. Coimbra JT, Feghali R, Ribeiro RP, Ramos MJ, Fernandes PA. The importance of intramolecular hydrogen bonds on the translocation of the small drug piracetam through a lipid bilayer. *RSC Advances*. 2021;11(2):899-908.
277. Desai PV, Raub TJ, Blanco MJ. How hydrogen bonds impact P-glycoprotein transport and permeability. *Bioorg Med Chem Lett*. 2012;22(21):6540-8.
278. Z OB, Moghaddam MF. A Systematic Analysis of Physicochemical and ADME Properties of All Small Molecule Kinase Inhibitors Approved by US FDA from January 2001 to October 2015. *Curr Med Chem*. 2017;24(29):3159-84.
279. Ritchie TJ, Ertl P, Lewis R. The graphical representation of ADME-related molecule properties for medicinal chemists. *Drug Discovery Today*. 2011;16(1-2):65-72.
280. Sharda S, Khandelwal R, Adhikary R, Sharma D, Majhi M, Hussain T, et al. A computer-aided drug designing for pharmacological inhibition of mutant ALK for the treatment of non-small cell lung cancer. *Current topics in medicinal chemistry*. 2019;19(13):1129-44.
281. Verma AK. Virtual screening, molecular docking, and ADME/T analysis of natural product library against cell invasion protein SipB from *Salmonella enterica* serotype typhi: in silico analysis. *Acta Scientific Pharmaceutical Sciences*. 2020;4(8):20-30.
282. Guengerich FP. Cytochrome p450 and chemical toxicology. *Chemical research in toxicology*. 2008;21(1):70-83.
283. König J, Müller F, Fromm MF. Transporters and drug-drug interactions: important determinants of drug disposition and effects. *Pharmacological reviews*. 2013;65(3):944-66.
284. Hameed A, Al-Rashida M, Uroos M, Ali SA, Arshia, Ishtiaq M, et al. Quinazoline and quinazolinone as important medicinal scaffolds: a comparative patent review (2011–2016). *Expert opinion on therapeutic patents*. 2018;28(4):281-97.
-

-
285. Selvam TP, Kumar PV. Quinazoline marketed drugs. *Research in Pharmacy*. 2015;1(1).
286. Zayed M, Hassan M. Design, synthesis and biological evaluation studies of novel quinazoline derivatives as cytotoxic agents. *Drug research*. 2013;63(04):210-5.
287. Pati B, Banerjee S. Quinazolines: an illustrated review. *Journal of Advanced Pharmacy Education & Research* Jul-Sept. 2013;3(3).
288. OECD. Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation. (ENV/JM/MONO (2000) 7). 2000.
289. Olfert E, Bhasin J, Latt R, McCutcheon K, Rainnie D, Schunk M. CCAC Guidelines on: Choosing an Appropriate Endpoint in Experiments Using Animals for Research, Teaching and Testing. 1998.
290. Rivas CAB, Castillo AA, Martínez HS, Zapata EP, Hernández JB, Tassé YM. Acute oral toxicity of *Azadirachta indica* (Neem Tree). *Revista Cubana de Plantas Medicinales*. 2013;18(3):502-7.
291. Guyenet PG. The sympathetic control of blood pressure. *Nature Reviews Neuroscience*. 2006;7(5):335-46.
292. Fujita T. Mechanism of salt-sensitive hypertension: focus on adrenal and sympathetic nervous systems. *Journal of the American Society of Nephrology*. 2014;25(6):1148-55.
293. Basting T, Lazartigues E. DOCA-salt hypertension: an update. *Current hypertension reports*. 2017;19(4):1-8.
294. Masi S, Uliana M, Virdis A. Angiotensin II and vascular damage in hypertension: Role of oxidative stress and sympathetic activation. *Vascular pharmacology*. 2019;115:13-7.
295. Bae EH, Kim IJ, Park JW, Ma SK, Lee JU, Kim SW. Renoprotective effect of rosuvastatin in DOCA-salt hypertensive rats. *Nephrology Dialysis Transplantation*. 2010;25(4):1051-9.
296. Lindoso RS, Lopes JA, Binato R, Abdelhay E, Takiya CM, de Miranda KR, et al. Adipose mesenchymal cells-derived EVs alleviate DOCA-salt-induced hypertension by promoting cardio-renal protection. *Molecular Therapy-Methods & Clinical Development*. 2020;16:63-77.
297. Basting T, Lazartigues E. DOCA-salt hypertension: an update. *Current hypertension reports*. 2017;19(4):32.
298. Kee HJ, Bae EH, Park S, Lee KE, Suh SH, Kim SW, et al. HDAC inhibition suppresses cardiac hypertrophy and fibrosis in DOCA-salt hypertensive rats via regulation of

-
- HDAC6/HDAC8 enzyme activity. *Kidney and Blood Pressure Research*. 2013;37(4-5):229-39.
299. Grobe JL, Mecca AP, Mao H, Katovich MJ. Chronic angiotensin-(1–7) prevents cardiac fibrosis in DOCA-salt model of hypertension. *American Journal of Physiology-Heart and Circulatory Physiology*. 2006;290(6):H2417-H23.
300. Kirchhoff F, Krebs C, Abdulhag U, Meyer-Schwesinger C, Maas R, Helmchen U, et al. Rapid development of severe end-organ damage in C57BL/6 mice by combining DOCA salt and angiotensin II. *Kidney international*. 2008;73(5):643-50.
301. Nishikawa K. Angiotensin AT1 receptor antagonism and protection against cardiovascular end-organ damage. *Journal of human hypertension*. 1998;12(5):301-9.
302. Muñoz-Durango N, Fuentes CA, Castillo AE, González-Gómez LM, Vecchiola A, Fardella CE, et al. Role of the renin-angiotensin-aldosterone system beyond blood pressure regulation: molecular and cellular mechanisms involved in end-organ damage during arterial hypertension. *International journal of molecular sciences*. 2016;17(7):797.
303. Schenk J, McNeill JH. The pathogenesis of DOCA-salt hypertension. *Journal of pharmacological and toxicological methods*. 1992;27(3):161-70.
304. Gomes PM, Sá RWM, Aguiar GL, Paes MHS, Alzamora AC, Lima WG, et al. Chronic high-sodium diet intake after weaning lead to neurogenic hypertension in adult Wistar rats. *Scientific reports*. 2017;7(1):1-14.
305. O'Donoghue TL, Qi Y, Brooks VL. Central action of increased osmolality to support blood pressure in deoxycorticosterone acetate–salt rats. *Hypertension*. 2006;48(4):658-63.
306. Stachenfeld NS. Acute effects of sodium ingestion on thirst and cardiovascular function. *Current sports medicine reports*. 2008;7(4 Suppl):S7.
307. O'Donoghue TL, Brooks VL. Deoxycorticosterone acetate–salt rats: hypertension and sympathoexcitation driven by increased NaCl levels. *Hypertension*. 2006;47(4):680-5.
308. Brooks VL, Scrogin KE, McKEOGH DF. The interaction of angiotensin II and osmolality in the generation of sympathetic tone during changes in dietary salt intake: an hypothesis. *Annals of the New York Academy of Sciences*. 2001;940(1):380-94.
309. Brooks VL, Haywood JR, Johnson AK. Translation of salt retention to central activation of the sympathetic nervous system in hypertension. *Clinical and experimental pharmacology and physiology*. 2005;32(5-6):426-32.

-
310. Wang Q, Domenighetti AA, Pedrazzini T, Burnier M. Potassium supplementation reduces cardiac and renal hypertrophy independent of blood pressure in DOCA/salt mice. *Hypertension*. 2005;46(3):547-54.
311. Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nature Reviews Nephrology*. 2013;9(8):459-69.
312. Khan M, Hye A, Neckář J, Cummins B, Wahl GM, Imig JD. Azilsartan decreases renal and cardiovascular injury in the spontaneously hypertensive obese rat. *Cardiovascular drugs and therapy*. 2014;28(4):313-22.
313. Wang D, Luo Y, Myakala K, Orlicky DJ, Dobrinskikh E, Wang X, et al. Serelaxin improves cardiac and renal function in DOCA-salt hypertensive rats. *Scientific reports*. 2017;7(1):1-10.
314. Loch D, Hoey A, Morisseau C, Hammock BO, Brown L. Prevention of hypertension in DOCA-salt rats by an inhibitor of soluble epoxide hydrolase. *Cell biochemistry and biophysics*. 2007;47(1):87-97.
315. Seifi B, Kadkhodae M, Karimian SM, Zahmatkesh M, Xu J, Soleimani M. Evaluation of renal oxidative stress in the development of DOCA-salt induced hypertension and its renal damage. *Clinical and experimental hypertension*. 2010;32(2):90-7.
316. Yemane H, Busauskas M, Burris SK, Knuepfer MM. Neurohumoral mechanisms in deoxycorticosterone acetate (DOCA)-salt hypertension in rats. *Experimental physiology*. 2010;95(1):51-5.
317. Eid H, De Champlain J. Increased inositol monophosphate production in cardiovascular tissues of DOCA-salt hypertensive rats. *Hypertension*. 1988;12(2):122-8.
318. Reid JL, Zivin JA, Kopin IJ. Central and peripheral adrenergic mechanisms in the development of deoxycorticosterone-saline hypertension in rats. *Circulation research*. 1975;37(5):569-79.
319. Kang K-T. Endothelium-derived relaxing factors of small resistance arteries in hypertension. *Toxicological research*. 2014;30(3):141-8.
320. Hernandez N, Torres SH, De Sanctis JB, Sosa A. Metabolic changes in DOCA-salt hypertensive rats. *Research communications in molecular pathology and pharmacology*. 2000;108(3-4):201-11.
321. Patil CN, Ritter ML, Wackman KK, Oliveira V, Balapattabi K, Grobe CC, et al. Cardiometabolic effects of DOCA-salt in male C57BL/6J mice are variably dependent on

-
- sodium and nonsodium components of diet. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2022;322(6):R467-R85.
322. Grobe JL, Buehrer BA, Hilzendeger AM, Liu X, Davis DR, Xu D, et al. Angiotensinergic signaling in the brain mediates metabolic effects of deoxycorticosterone (DOCA)-salt in C57 mice. *Hypertension*. 2011;57(3):600-7.
323. Bender SB, McGraw AP, Jaffe IZ, Sowers JR. Mineralocorticoid receptor-mediated vascular insulin resistance: an early contributor to diabetes-related vascular disease? *Diabetes*. 2013;62(2):313-9.
324. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bäracker L, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *Journal of cardiovascular pharmacology*. 2014;64(1):69-78.
325. Garg R, Adler GK. Role of mineralocorticoid receptor in insulin resistance. *Current Opinion in Endocrinology, Diabetes and Obesity*. 2012;19(3):168-75.
326. Favero G, Paganelli C, Buffoli B, Rodella LF, Rezzani R. Endothelium and its alterations in cardiovascular diseases: life style intervention. *BioMed research international*. 2014;2014.
327. DE GRACIA MC, Osuna A, O'VALLE F, Del Moral RG, Wangenstein R, Del Rio CG, et al. Deoxycorticosterone Suppresses the Effects of Losartan in Nitric Oxide—Deficient Hypertensive Rats. *Journal of the American Society of Nephrology*. 2000;11(11):1995-2000.
328. Kim J, Lee YR, Lee C-H, Choi W-H, Lee C-K, Kim J, et al. Mitogen-activated protein kinase contributes to elevated basal tone in aortic smooth muscle from hypertensive rats. *European journal of pharmacology*. 2005;514(2-3):209-15.
329. Henrion D, Laher I, Laporte R, Bevan JA. Angiotensin II amplifies arterial contractile response to norepinephrine without increasing Ca^{++} influx: Role of protein kinase C. *Journal of Pharmacology and Experimental Therapeutics*. 1992;261(3):835-40.
330. Barnes PJ. Receptor heterodimerization: a new level of cross-talk. *The Journal of clinical investigation*. 2006;116(5):1210-2.
331. Northcott CA, Hayflick JS, Watts SW. PI3-Kinase upregulation and involvement in spontaneous tone in arteries from DOCA-salt rats: is p110 δ the culprit? *Hypertension*. 2004;43(4):885-90.
332. Northcott CA, Poy MN, Najjar SM, Watts SW. Phosphoinositide 3-kinase mediates enhanced spontaneous and agonist-induced contraction in aorta of deoxycorticosterone acetate-salt hypertensive rats. *Circulation research*. 2002;91(4):360-9.
-

-
333. Kim K-I, Lee J-H, Chang H-J, Cho Y-S, Youn T-J, Chung W-Y, et al. Association between blood pressure variability and inflammatory marker in hypertensive patients. *Circulation Journal*. 2008;72(2):293-8.
334. Santisteban MM, Ahmari N, Carvajal JM, Zingler MB, Qi Y, Kim S, et al. Involvement of bone marrow cells and neuroinflammation in hypertension. *Circulation research*. 2015;117(2):178-91.
335. Harrison D. Sy 17-2 inflammation, immunity and hypertension. *Journal of hypertension*. 2016;34:e535.
336. Tanase DM, Gosav EM, Radu S, Ouatu A, Rezus C, Ciocoiu M, et al. Arterial hypertension and interleukins: potential therapeutic target or future diagnostic marker? *International journal of hypertension*. 2019;2019.
337. Song K, Stuart D, Abraham N, Wang F, Wang S, Yang T, et al. Collecting duct renin does not mediate DOCA-salt hypertension or renal injury. *PLoS One*. 2016;11(7):e0159872.
338. Artunc F, Amann K, Nasir O, Friedrich B, Sandulache D, Jahovic N, et al. Blunted DOCA/high salt induced albuminuria and renal tubulointerstitial damage in gene-targeted mice lacking SGK1. *Journal of molecular medicine*. 2006;84(9):737-46.
339. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. *Kidney international*. 2003;63(5):1791-800.
340. Jia Z, Aoyagi T, Yang T. mPGES-1 protects against DOCA-salt hypertension via inhibition of oxidative stress or stimulation of NO/cGMP. *Hypertension*. 2010;55(2):539-46.
341. Quigley R, Chakravarty S, Zhao X, Imig JD, Capdevila JH. Increased renal proximal convoluted tubule transport contributes to hypertension in Cyp4a14 knockout mice. *Nephron Physiology*. 2009;113(4):p23-p8.
342. Jennings GL. Recent clinical trials of hypertension management. *Hypertension*. 2013;62(1):3-7.
343. Sahan-Firat S, Jennings BL, Yaghini FA, Song CY, Estes AM, Fang XR, et al. 2, 3', 4, 5'-Tetramethoxystilbene prevents deoxycorticosterone-salt-induced hypertension: contribution of cytochrome P-450 1B1. *American Journal of Physiology-Heart and Circulatory Physiology*. 2010;299(6):H1891-H901.
344. Welch WJ, Baumgärtl H, Lübbers D, Wilcox CS. Renal oxygenation defects in the spontaneously hypertensive rat: role of AT1 receptors. *Kidney international*. 2003;63(1):202-8.
-

-
345. Seifi B, Kadkhodaei M, Karimian SM, Zahmatkesh M, Xu J, Soleimani MJC, et al. Evaluation of renal oxidative stress in the development of DOCA-salt induced hypertension and its renal damage. 2010;32(2):90-7.
346. Nishiyama A, Yao L, Nagai Y, Miyata K, Yoshizumi M, Kagami S, et al. Possible contributions of reactive oxygen species and mitogen-activated protein kinase to renal injury in aldosterone/salt-induced hypertensive rats. *Hypertension*. 2004;43(4):841-8.
347. Li J-M, Shah AM. Mechanism of endothelial cell NADPH oxidase activation by angiotensin II: role of the p47phox subunit. *Journal of Biological Chemistry*. 2003;278(14):12094-100.
348. Chen Z, Wu C, Liu Y, Li H, Zhu Y, Huang C, et al. ELABELA attenuates deoxycorticosterone acetate/salt-induced hypertension and renal injury by inhibition of NADPH oxidase/ROS/NLRP3 inflammasome pathway. *Cell Death & Disease*. 2020;11(8):1-15.
349. Laplante M-A, De Champlain J. The interrelation of the angiotensin and endothelin systems on the modulation of NAD (P) H oxidase. *Canadian journal of physiology and pharmacology*. 2006;84(1):21-8.
350. Irshad N, Khan A-u, Iqbal MSJB, Pharmacotherapy. Antihypertensive potential of selected pyrimidine derivatives: explanation of underlying mechanistic pathways. 2021;139:111567.
351. Safaeian L, Emami R, Hajhashemi V, Haghighatian ZJB, Pharmacotherapy. Antihypertensive and antioxidant effects of protocatechuic acid in deoxycorticosterone acetate-salt hypertensive rats. 2018;100:147-55.
352. Martinez-Quinones P, McCarthy CG, Watts SW, Klee NS, Komic A, Calmasini FB, et al. Hypertension induced morphological and physiological changes in cells of the arterial wall. 2018;31(10):1067-78.
353. Lockette W, Otsuka Y, Carretero O. The loss of endothelium-dependent vascular relaxation in hypertension. *Hypertension*. 1986;8(6_pt_2):II61.
354. Pollock DM, Polakowski JS, Divish BJ, Opgenorth TJ. Angiotensin blockade reverses hypertension during long-term nitric oxide synthase inhibition. *Hypertension*. 1993;21(5):660-6.
355. Sung JH, Jo YS, Kim SJ, Ryu JS, Kim MC, Ko HJ, et al. Effect of lutein on L-NAME-induced hypertensive rats. *The Korean Journal of Physiology & Pharmacology*. 2013;17(4):339-45.
-

-
356. Simko F, Baka T, Krajcirovicova K, Repova K, Aziriova S, Zorad S, et al. Effect of melatonin on the renin-angiotensin-aldosterone system in L-NAME-induced hypertension. *Molecules*. 2018;23(2):265.
357. Ajayi A, Hercule H, Pamugo J, Dixon D, Oyekan A. Interactions of the Renin–angiotensin System and Alpha-1 Adrenoceptors on Renal Hemodynamics in Healthy and Acute Renal Failure Rats: The Role of Nitric Oxide. *Blood pressure*. 2001;10(4):238-46.
358. Manning Jr RD, Hu L, Mizelle HL, Montani J-P, Norton MW. Cardiovascular responses to long-term blockade of nitric oxide synthesis. *Hypertension*. 1993;22(1):40-8.
359. Hollenberg SM, Broussard M, Osman J, Parrillo JE. Increased microvascular reactivity and improved mortality in septic mice lacking inducible nitric oxide synthase. *Circulation research*. 2000;86(7):774-8.
360. Sander M, Hansen PG, Victor RG. Sympathetically mediated hypertension caused by chronic inhibition of nitric oxide. *Hypertension*. 1995;26(4):691-5.
361. Curnow AC, Gonzalez SR, Gogulamudi VR, Visniauskas B, Simon EE, Gonzalez AA, et al. Low nitric oxide bioavailability increases renin production in the collecting duct. *Frontiers in Physiology*. 2020;11:559341.
362. Hsu C-N, Tain Y-L. Targeting the renin–angiotensin–aldosterone system to prevent hypertension and kidney disease of developmental origins. *International Journal of Molecular Sciences*. 2021;22(5):2298.
363. Li X, Yuasa S, Hitomi H, Hashimoto M, Fujioka H, Kiyomoto H, et al. Mechanism mediating hypertension induced by chronic inhibition of nitric oxide synthesis. *Nihon Jinzo Gakkai shi*. 1997;39(7):718-27.
364. Blanc J, Ponchon P, Laude D, Elghozi J-L, Jover B. Blood pressure variability in established L-NAME hypertension in rats. *Journal of hypertension*. 1999;17(11):1527-34.
365. Naruse K, Shimizu K, Muramatsu M, Toki Y, Miyazaki Y, Okumura K, et al. Long-term inhibition of NO synthesis promotes atherosclerosis in the hypercholesterolemic rabbit thoracic aorta. PGH2 does not contribute to impaired endothelium-dependent relaxation. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology*. 1994;14(5):746-52.
366. Miguel-Carrasco JL, Mate A, Monserrat MT, Arias JL, Aramburu O, Vázquez CM. The role of inflammatory markers in the cardioprotective effect of L-carnitine in L-NAME-induced hypertension. *American journal of hypertension*. 2008;21(11):1231-7.

-
367. Bachhav SS, Bhutada MS, Patil SP, Sharma KS, Patil SD. Oleanolic acid prevents increase in blood pressure and nephrotoxicity in nitric oxide dependent type of hypertension in rats. *Pharmacognosy Research*. 2015;7(4):385.
368. Redón J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. *Hypertension*. 2003;41(5):1096-101.
369. Briones AM, Touyz RM. Oxidative stress and hypertension: current concepts. *Current hypertension reports*. 2010;12(2):135-42.
370. Sowers JR. Diabetes mellitus and vascular disease. *Hypertension*. 2013;61(5):943-7.
371. Stroth U, Unger T. The renin-angiotensin system and its receptors. *Journal of cardiovascular pharmacology*. 1999;33:S21-S8.
372. Juarez E, Tufiño C, Querejeta E, Bracho-Valdes I, Bobadilla-Lugo RA. Evidence of changes in alpha-1/AT1 receptor function generated by diet-induced obesity. *Diabetes and Vascular Disease Research*. 2017;14(6):485-93.
373. Mayer MA, Höcht C, Gironacci M, Opezzo JA, Taira CA, Fernández BE, et al. Hypothalamic angiotensinergic–noradrenergic systems interaction in fructose induced hypertension. *Regulatory peptides*. 2008;146(1-3):38-45.
374. Jerez S, de Bruno María P, Alfredo C. Cross talk between angiotensin II and alpha 1 adrenergic receptors in rabbit aorta: role of endothelium. *Journal of cardiovascular pharmacology*. 2004;43(3):402-9.
375. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. *Hypertension*. 1987;10(5):512-6.
376. Reungjui S, Roncal CA, Mu W, Srinivas TR, Sirivongs D, Johnson RJ, et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. *Journal of the American Society of Nephrology*. 2007;18(10):2724-31.
377. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes care*. 1991;14(3):173-94.
378. DeFronzo R. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia*. 2010;53(7):1270-87.
379. Ibrahim SM, El-Denshary ES, Abdallah DM. Geraniol, alone and in combination with pioglitazone, ameliorates fructose-induced metabolic syndrome in rats via the modulation of both inflammatory and oxidative stress status. *PloS one*. 2015;10(2):e0117516.
-

-
380. Prince PD, Lanzi CR, Toblli JE, Elesgaray R, Oteiza PI, Fraga CG, et al. Dietary (–)-epicatechin mitigates oxidative stress, NO metabolism alterations, and inflammation in renal cortex from fructose-fed rats. *Free Radical Biology and Medicine*. 2016;90:35-46.
381. Dai S, McNeill JH. Fructose-induced hypertension in rats is concentration-and duration-dependent. *Journal of pharmacological and toxicological methods*. 1995;33(2):101-7.
382. Rendeiro C, Masnik AM, Mun JG, Du K, Clark D, Dilger RN, et al. Fructose decreases physical activity and increases body fat without affecting hippocampal neurogenesis and learning relative to an isocaloric glucose diet. *Scientific reports*. 2015;5(1):1-9.
383. Cabandugama PK, Gardner MJ, Sowers JR. The renin angiotensin aldosterone system in obesity and hypertension: roles in the cardiorenal metabolic syndrome. *Medical Clinics*. 2017;101(1):129-37.
384. Komnenov D, Levanovich PE, Rossi NF. Hypertension associated with fructose and high salt: renal and sympathetic mechanisms. *Nutrients*. 2019;11(3):569.
385. Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. *American Journal of Physiology-Heart and Circulatory Physiology*. 2012;302(6):H1219-H30.
386. Gill H, Mugo M, Whaley-Connell A, Stump C, Sowers JR. The key role of insulin resistance in the cardiometabolic syndrome. *The American journal of the medical sciences*. 2005;330(6):290-4.
387. McCarty MF. Elevated sympathetic activity may promote insulin resistance syndrome by activating alpha-1 adrenergic receptors on adipocytes. *Medical hypotheses*. 2004;62(5):830-8.
388. Barthel A, Nakatani K, Dandekar AA, Roth RA. Protein kinase C modulates the insulin-stimulated increase in Akt1 and Akt3 activity in 3T3-L1 adipocytes. *Biochemical and biophysical research communications*. 1998;243(2):509-13.
389. Cortright RN, Azevedo Jr JL, Zhou Q, Sinha M, Pories WJ, Itani SI, et al. Protein kinase C modulates insulin action in human skeletal muscle. *American Journal of Physiology-Endocrinology And Metabolism*. 2000;278(3):E553-E62.
390. Natarajan A, Van Anthony MV, Jose PA. Renal Modulation: The Renin-Angiotensin System. *Nephrology and Fluid/electrolyte Physiology: Elsevier*; 2019. p. 165-88.

-
391. Kamari Y, Harari A, Shaish A, Peleg E, Sharabi Y, Harats D, et al. Effect of telmisartan, angiotensin II receptor antagonist, on metabolic profile in fructose-induced hypertensive, hyperinsulinemic, hyperlipidemic rats. *Hypertension Research*. 2008;31(1):135-40.
392. Mather KJAjop-e, metabolism. Surrogate measures of insulin resistance: of rats, mice, and men. 2009;296(2):E398-E9.
393. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. *Indian journal of endocrinology and metabolism*. 2015;19(1):160.
394. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. 2013;13(1):1-10.
395. Farag MM, Ashour EH, El-Hadidy WFJDMJ. Amelioration of High Fructose Diet-Induced Insulin Resistance, Hyperuricemia, and Liver Oxidative Stress by Combined Use of Selective Agonists of PPAR- α and PPAR- γ in Rats. 2020;3(2):76-86.
396. Thomas S, Senthilkumar GP, Sivaraman K, Bobby Z, Paneerselvam S, Harichandrakumar KTJJjoms. Effect of s-methyl-L-cysteine on oxidative stress, inflammation and insulin resistance in male wistar rats fed with high fructose diet. 2015;40(1):45.
397. Eren OC, Ortiz A, Afsar B, Covic A, Kuwabara M, Lanaspa MA, et al. Multilayered interplay between fructose and salt in development of hypertension: what has been revealed so far. *Hypertension*. 2019;73(2):265-72.
398. Armitage JA, Burke SL, Prior LJ, Barzel B, Eikelis N, Lim K, et al. Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. *Hypertension*. 2012;60(1):163-71.
399. Zemančíková A, Török J. Cardiovascular effects of high-fructose intake in rats with nitric oxide deficiency. *Interdisciplinary toxicology*. 2014;7(3):159-64.
400. Eichler H-G, Ford GA, Blaschke TF, Swislocki A, Hoffman B. Responsiveness of superficial hand veins to phenylephrine in essential hypertension. Alpha adrenergic blockade during prazosin therapy. *The Journal of Clinical Investigation*. 1989;83(1):108-12.
401. Hartwig CL, Sprick JD, Jeong J, Hu Y, Morison DG, Stein CM, et al. Increased vascular α 1-adrenergic receptor sensitivity in older adults with posttraumatic stress disorder. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2020;319(6):R611-R6.
-

-
402. Sprick JD, Morison DL, Stein CM, Li Y, Paranjape S, Fonkoue IT, et al. Vascular α 1-adrenergic sensitivity is enhanced in chronic kidney disease. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2019;317(3):R485-R90.
403. Zhang D-M, Jiao R-Q, Kong L-D. High dietary fructose: direct or indirect dangerous factors disturbing tissue and organ functions. *Nutrients*. 2017;9(4):335.
404. Kovačević S, Brkljačić J, Milutinović DV, Gligorovska L, Bursać B, Elaković I, et al. Fructose Induces Visceral Adipose Tissue Inflammation and Insulin Resistance Even Without Development of Obesity in Adult Female but Not in Male Rats. *Frontiers in nutrition*. 2021;8.
405. Chou C-L, Lin H, Chen J-S, Fang T-C. Renin inhibition improves metabolic syndrome, and reduces angiotensin II levels and oxidative stress in visceral fat tissues in fructose-fed rats. *PloS one*. 2017;12(7):e0180712.
406. Sharabi Y, Oron-Herman M, Kamari Y, Avni I, Peleg E, Shabtay Z, et al. Effect of PPAR- γ agonist on adiponectin levels in the metabolic syndrome: lessons from the high fructose fed rat model. *American journal of hypertension*. 2007;20(2):206-10.
407. Mamikutty N, Thent ZC, Haji Suhaimi F. Fructose-drinking water induced nonalcoholic fatty liver disease and ultrastructural alteration of hepatocyte mitochondria in male Wistar rat. *BioMed research international*. 2015;2015.
408. Liang Z, Li QX. π -Cation interactions in molecular recognition: Perspectives on pharmaceuticals and pesticides. *Journal of agricultural and food chemistry*. 2018;66(13):3315-23.
409. Patel NR, Patel DV, Kanhed AM, Patel SP, Patel KV, Afosah DK, et al. 2-Aminobenzamide-Based Factor Xa Inhibitors with Novel Mono-and Bi-Aryls as S4 Binding Elements. *ChemistrySelect*. 2019;4(3):802-9.
410. Rai R, Sprengeler P, Elrod K, Young W. Perspectives on factor Xa inhibition. *Current medicinal chemistry*. 2001;8(2):101-19.
411. Pinto DJ, Smallheer JM, Cheney DL, Knabb RM, Wexler RR. Factor Xa inhibitors: next-generation antithrombotic agents. *Journal of medicinal chemistry*. 2010;53(17):6243-74.
412. De Cristofaro R, De Candia E. Thrombin domains: structure, function and interaction with platelet receptors. *Journal of thrombosis and thrombolysis*. 2003;15(3):151-63.
413. Zhang Y, Li L, Zhao Y, Han H, Hu Y, Liang D, et al. The myosin II inhibitor, blebbistatin, ameliorates FeCl₃-induced arterial thrombosis via the GSK3 β -NF- κ B pathway. *International journal of biological sciences*. 2017;13(5):630.
-

-
414. Barr JD, Chauhan AK, Schaeffer GV, Hansen JK, Motto DG. Red blood cells mediate the onset of thrombosis in the ferric chloride murine model. *Blood, The Journal of the American Society of Hematology*. 2013;121(18):3733-41.
415. Wang L, Miller C, Swarthout RF, Rao M, Mackman N, Taubman MB. Vascular smooth muscle-derived tissue factor is critical for arterial thrombosis after ferric chloride-induced injury. *Blood, The Journal of the American Society of Hematology*. 2009;113(3):705-13.
416. Eckly A, Hechler B, Freund M, Zerr M, Cazenave JP, Lanza F, et al. Mechanisms underlying FeCl₃-induced arterial thrombosis. *Journal of Thrombosis and Haemostasis*. 2011;9(4):779-89.
417. Li W, Nieman M, Gupta AS. Ferric chloride-induced murine thrombosis models. *JoVE (Journal of Visualized Experiments)*. 2016(115):e54479.
418. Tseng MT, Dozier A, Haribabu B, Graham UM. Transendothelial migration of ferric ion in FeCl₃ injured murine common carotid artery. *Thrombosis research*. 2006;118(2):275-80.
419. Li W, McIntyre TM, Silverstein RL. Ferric chloride-induced murine carotid arterial injury: A model of redox pathology. *Redox biology*. 2013;1(1):50-5.
420. Hanson SR, Harker LA, Ratner BD, Hoffman AS. In vivo evaluation of artificial surfaces with a nonhuman primate model of arterial thrombosis. *The Journal of laboratory and clinical medicine*. 1980;95(2):289-304.
421. Yu C, Qi D, Lian W, Li Q-Z, Li H-J, Fan H-Y. Effects of danshensu on platelet aggregation and thrombosis: in vivo arteriovenous shunt and venous thrombosis models in rats. *PloS one*. 2014;9(11):e110124.
422. Furugohri T, Isobe K, Honda Y, Kamisato-Matsumoto C, Sugiyama N, Nagahara T, et al. DU-176b, a potent and orally active factor Xa inhibitor: in vitro and in vivo pharmacological profiles. *Journal of Thrombosis and Haemostasis*. 2008;6(9):1542-9.
423. Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer KH, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor. *Journal of Thrombosis and Haemostasis*. 2005;3(3):514-21.