

SHORT COMMUNICATION

THE EFFECTS OF XANTHINE OXIDASE INHIBITORS ON THE MANAGEMENT OF CARDIOVASCULAR DISEASES

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Cardiovascular diseases (CVDs) are the fastest-growing cause of death around the world, and atherosclerosis plays a major role in the etiology of CVDs. The most recent figures show that the total number of CVD patients worldwide surged from 271 million in 1990 to 523 million in 2019. Furthermore, globally, the number of fatalities caused by coronary artery disease (CAD) went up from 1.2 million in 1990 to 18.6 million in 2019.¹ The morbidity and mortality rates for patients with heart failure (HF) are still too high, despite being given the therapy according to the recommended guidelines.² HF strains the public health system, so better treatment options are required. According to different studies, in HF, the manifestation of ventricular and vascular remodeling, as well as the progression of the illness, may be influenced by elevated oxidative stress.^{3,4} The most prevalent form of inflammatory arthritis in the world, gout, correlates with CVDs and is a standalone predictor of all-cause death.^{5,6} An important therapeutic target and potential contributor to oxidative stress is the enzyme xanthine oxidase (XO). Oxidative stress is a state in which there is excessive production of reactive oxygen species (ROS). The key generators of ROS are oxidant-producing enzymes, which are increased in various disease conditions.⁷ Superoxide and uric acid (UA) are produced due to increased XO activity during purine metabolism. In addition to being the primary cause of gout, elevated xanthine oxidase is also to blame for several clinical illnesses linked to hyperuricemia, such as cardiovascular disorders, diabetes, chronic wounds, and Alzheimer's disease. Numerous studies have shown a direct connection between high urate levels and CVDs. The generation of urate crystals is a complicated process. Since the same enzyme that makes urate also causes the creation of ROS. According to some research, the urate molecule can scavenge *in vitro* free radicals and acute urate infusions help at-risk population restore their endothelial function.^{8,9} More and more evidence suggests that XO activity plays a significant role in target organ damage and tissue destruction rather than UA itself. The formation of UA requires the xanthine oxidoreductase (XOR) enzyme, and XOR is composed of XO and xanthine dehydrogenase (XDH). By posttranslational modification, XDH is transformed into XO, which catalyzes the final two steps of the

processes that change hypoxanthine into xanthine and xanthine into UA. During this process, superoxide and hydrogen peroxide are produced. As a result, ROS can be produced when XO is activated, which might cause tissue damage. Nitric oxide (NO) and circulating XO can directly interact when the latter binds to vascular cells, causing NO levels to drop and peroxynitrite levels to rise. On the other hand, uric acid transporters (UATs) have been identified to mediate the effects of serum UA on vascular endothelial cells or smooth muscle cells, as URAT1 is only expressed on these cells and provides a route for UA to access these cells. By delaying NO generation and accelerating its breakdown, UA reduces NO levels when it enters endothelial cells.⁴ The organic anion transport inhibitor probenecid prevents UA-induced vascular smooth muscle cell proliferation. It reduces the generation of NO in human umbilical vein endothelial cells, suggesting that UATs are the mechanism via which UA exerts its impact.⁵ These findings pose the concern of whether the reduction in serum UA or the suppression of XO activity is more crucial for preventing cardiovascular and other tissue damage. However, in *in vivo* studies, UA performs pro- and antioxidant functions. When serum UA concentrations rise beyond 6 mg/dL, UA is taken up by vascular endothelial cells, which then triggers nicotinamide adenine dinucleotide phosphate oxidase to produce reactive oxygen species (ROS). Additionally, UA causes the apoptosis of vascular endothelial cells at levels of 9 mg/dL and higher. In other words, an excessively significant increase in the serum UA level might cause oxidative stress, alter the equilibrium between oxidation and antioxidants, and result in damage to vascular endothelial cells.¹⁰ Previous studies have shown that severe hyperuricemia, which lowers ejection fraction and is related to symptoms even worse, exercise intolerance, and decreased survival, is present in about 25% of individuals with heart failure (HF).^{11,12} Serum UA levels must be considered when calculating HF risk scores and may be used to identify high-risk patients for potential XO inhibition therapy.^{13,14} The approved treatment regimens for gout have significant implications for individuals with cardiovascular disease (CVD) due to varied levels of cardiovascular and HF benefits and risks. Therefore, it is essential to treat acute gout flares while reducing the risk of severe cardiovascular events

and managing hyperuricemia using urate-lowering treatment.¹⁵ Allopurinol is a powerful XO inhibitor that can potentially reverse several HF pathophysiological processes, including impaired calcium sensitivity, accelerated anaerobic metabolism, mechanoenergetic uncoupling, and energy depletion. Allopurinol has been found in studies to improve cardiac efficiency and decrease oxygen consumption in both animals and humans with HF.^{16,17} Allopurinol, febuxostat, and topiroxostat, the commonly prescribed xanthine oxidase inhibitors used in clinical practice, suffer from fatal side effects that constitute a severe dilemma for the healthcare system and have sparked a global emergency to find novel, potent, and safer xanthine oxidase inhibitors.⁹ Herbal medications are utilized worldwide due to their effectiveness, affordability, accessibility, and safety.¹⁸ The conventional medical community holds colchicine in the highest regard. Colchicine's uses have been expanded from the treatment of gout to CVDs due to its special anti-inflammatory qualities and recent knowledge of chronic inflammation's role in several human diseases.¹ According to contemporary therapeutic jargon, Colchicine's recent use in the setting of CVDs is an example of successful pharmacological repurposing. Pericarditis is now considered to be included in routine treatment, and its impact on coronary artery disease, postpericardiotomy syndrome, and percutaneous coronary interventions has been the subject of numerous clinical studies. Several effective clinical trials have expanded our understanding of reducing inflammation in the management of cardiovascular disease and given us new perspectives on how inflammation affects CVDs.¹⁹ Future research towards safer and more efficient ways to treat CVDs is encouraged. Herbal remedies are a viable choice since they are accessible, safe, and efficient; however, further research is required to determine whether they can be used to treat CVDs in gout and hyperuricemia patients.¹⁸

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REFERENCES

- Zhang F-S, He Q-Z, Qin CH, Little PJ, Weng J-P, Xu S-W. Therapeutic potential of colchicine in cardiovascular medicine: a pharmacological review. *Acta Pharma Sinica*. 2022;43(9):2173-90.
- Chen J, Normand S-LT, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. *JAMA*. 2011;306(15):1669-78.
- Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol*. 2011;301(6):H2181-H90.
- Ashiq K, Ashiq S, Shehzadi N. Hyperuricemia and its association with hypertension: risk factors and management. *Pak Heart J*. 2022;55(2):200-1.
- Abhijit D, Bhaskar G, Jitendra ND. Traditional phytotherapy against skin diseases and in wound healing of the tribes of Purulia district, West Bengal, India *J Med Plants Res*. 2012;6(33):4825-483.
- A comprehensive review on gout: The epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment. *J Pak Med Assoc*. 2021;71(4):1234-8.
- Bergamini C, Ciccoira M, Rossi A, Vassanelli C. Oxidative stress and hyperuricaemia: pathophysiology, clinical relevance, and therapeutic implications in chronic heart failure. *Eur J Heart Fail*. 2009;11(5):444-52.
- George J, Struthers AD. The role of urate and xanthine oxidase inhibitors in cardiovascular disease. *Cardiovascular Drug Rev*. 2008;26(1):59-64.
- Singh A, Singh K, Sharma A, Kaur K, Chadha R, Bedi PMS. Past, Present and Future of Xanthine Oxidase Inhibitors: Design Strategies, Structural and Pharmacological Insights, Patents and Clinical Trials. *RSC Med Chem*. 2023;14(11):2155-91.
- Sekizuka H. Uric acid, xanthine oxidase, and vascular damage: potential of xanthine oxidoreductase inhibitors to prevent cardiovascular diseases. *Hypertension Res*. 2022;45(5):772-4.
- Karantalis V, Schulman IH, Hare JM. Nitroso-redox imbalance affects cardiac structure and function. *American College of Cardiology Foundation Washington, DC*; 2013. p. 933-5.
- Kittleson MM, St John ME, Bead V, Champion HC, Kasper EK, Russell SD, et al. Increased levels of uric acid predict haemodynamic compromise in patients with heart failure independently of B-type natriuretic peptide levels. *Heart*. 2007;93(3):365-7.
- Ky B, French B, Levy WC, Sweitzer NK, Fang JC, Wu AH, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circulation: Heart Failure*. 2012;5(2):183-90.
- Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113(11):1424-33.
- Mouradjian MT, Plazak ME, Gale SE, Noel ZR, Watson K, Devabhakthuni S. Pharmacologic management of gout in patients with cardiovascular disease and heart failure. *Am J Cardiovasc Drugs*. 2020;20(5):431-45.
- Cappola TP, Kass DA, Nelson GS, Berger RD, Rosas GO, Kobeissi ZA, et al. Allopurinol improves

- myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation*. 2001;104(20):2407-11.
17. Murphy R, Dutka T, Lamb G. Hydroxyl radical and glutathione interactions alter calcium sensitivity and maximum force of the contractile apparatus in rat skeletal muscle fibres. *J Physiol*. 2008;586(8):2203-16.
18. Ashiq K, Hussain K, Islam M, Shehzadi N, Ali E, Ashiq S. Medicinal plants of Pakistan and their xanthine oxidase inhibition activity to treat gout: a systematic review. *Turkish J Bot*. 2021;45(8):723-38.
19. Deftereos SG, Beerkens FJ, Shah B, Giannopoulos G, Vrachatis DA, Giotaki SG, et al. Colchicine in cardiovascular disease: in-depth review. *Circulation*. 2022;145(1):61-78.

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