MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Medicinal and Analytical Chemistry International Journal
ISSN: 2639-2534

# Trimetazidine: An Antianginal Drug and Not Only!

**Alrouhayyah R[1,2]* and Suslina SN[1]**

[1]Department of General Pharmaceutical and Biomedical Technology, Medical Institute, Peoples' Friendship University of Russia named after Patrice Lumumba (RUDN University), Moscow, Russian Federation

[2]Department of Analytical and Food Chemistry, Faculty of pharmacy, Damascus University, Damascus, Syria

**Mini Review**

**Volume 8 Issue 1**

**Received Date:** March 22, 2024

**Published Date:** May 08, 2024

DOI: 10.23880/macij-16000194

***Corresponding author:** Ranim Alrouhayyah, Department of General Pharmaceutical and Biomedical Technology, Medical Institute, Peoples' Friendship University of Russia named after Patrice Lumumba (RUDN University), 6 Miklukho-Maklaya street, Moscow, 117198, Russian Federation, Email: alrukhaie_r@pfur.ru

## Abstract

Trimetazidine, a piperazine derivative, has been in use for a long time as a safe drug in the long-term treatment of chronic ischemic disorders. The mechanism of action is basically that it partially inhibits mitochondrial fatty acid β-oxidation by blocking long-chain 3-ketoacyl-CoA thiolase and simultaneously enhances glucose oxidation, which means less oxygen consumption and increased mitochondrial efficiency by producing more adenosine triphosphate per mole of oxygen through glucose oxidation. However, as a metabolic modulator, the potency of trimetazidine has been studied to treat several diseases or disorders, which are considered to be caused by metabolic disorders. In this review, we highlight some of the studies that aimed to investigate the role of trimetazidine in treating some of these diseases, namely amyotrophic lateral sclerosis, statin-induced skeletal muscle damage, and cardiomyopathy and peripheral arterial diseases, namely amyotrophic lateral sclerosis, statin-induced skeletal muscle damage, and cardiomyopathy and peripheral arterial disease associated with diabetes.

**Keywords:** Trimetazidine; Metabolic Agent; Angina; Diabetes; COVID-19

**Abbreviations:** TMD: Trimetazidine; ICM: Ischemic Cardiomyopathy; ATP: Adenosine Triphosphate; ALS: Amyotrophic Lateral Sclerosis; NMJs: Neuromuscular Junctions; CHD: Coronary Heart Disease; DCM: Diabetic Cardiomyopathy; Nox2: NADPH Oxidase 2; TRPC3: Transient Receptor Potential Channel 3; STZ: Streptozocin; AGEs: Advanced Glycation End Products; TRPC3: Transient Receptor Potential Channel 3; PAD: Peripheral Arterial Disease; FAL: Femoral Artery Ligation; VEGF: Vascular Endothelial Growth Factor; ICAM-1: Intercellular Adhesion Molecule 1; ACI: Acute Cardiac Injury; Nrf2: Nuclear Factor Erythroid-Related 2; NF-κB: Nuclear Factor Kappa B; TNF-α: Tumor Necrosis Factor Alpha.

## Introduction

In 1969, trimetazidine (TMD), a piperazine derivative, was synthesized in Servier Laboratories (France) [1]. Since 1978 TMD has become, due to its significant anti-ischemic properties, a standard treatment for ischemic cardiomyopathy (ICM) as monotherapy or adjuvant therapy [2]. For the time being, TMD is prescribed as a long-term treatment for angina in more than 90 countries around the world. Disturbances in myocardial energy metabolism precede the morphological changes typical of ventricular hypertrophy. As cardiac hypertrophy develops, energy metabolism in hypertrophied cardiomyocytes changes from

aerobic oxidation to anaerobic fermentation [3]. Metabolic therapy aims to improve energy metabolism so that cardiac muscle cells can obtain more energy [4].

TMD is a metabolic factor that has protective effects on cardiac myocytes. It improves energy utilization by cardiomyocytes and maintains adequate energy supply during ischemia. There are several proposed mechanisms of action of TMD mainly involving cardioprotection by inhibiting oxidative stress, scavenging oxygen free radicals, improving lipid metabolism and mitochondrial function, and maintaining reperfusion. Myocardial ischemia and ventricular dysfunction lead to significant changes in mitochondrial oxidative metabolism, including an increase in the rate of cytoplasmic anaerobic glycolysis to compensate for the decrease in mitochondrial adenosine triphosphate (ATP) production. The remainder of mitochondrial oxidative metabolism results mainly from the oxidation of free fatty acids, resulting from glucose oxidation.

TMD partially inhibits mitochondrial fatty acid oxidation by blocking long-chain 3-ketoacyl-CoA thiolase and simultaneously enhances glucose oxidation, increasing mitochondrial efficiency by producing more ATP per mole of oxygen through glucose oxidation [5]. This reduces the side effects of oxidative stress associated with free fatty acids [6]. It also directs free fatty acids to the synthesis of phospholipids, which are involved in building the cell membrane [7]. In addition, TMD improves insulin sensitivity, increasing myocardial glucose uptake and promoting glucose oxidation [8]. Furthermore, TMD supports the contractile function of the myocardium, ensuring the operation of ionic pumps and the flux of sodium and potassium across the membrane, while maintaining cellular homeostasis [9]. Thus, TMD may protect myocardial ultrastructure and potentially prevent cardiac hypertrophy by improving the cell environment and promoting membrane synthesis [10].

However, being a nonspecific metabolic agent, TMD has been the subject of many studies to investigate its potential effects and prospects for use in the treatment of various diseases or disorders associated with energy imbalance or metabolic disorders. In this review, we would like to summarize some of these studies, namely studies examining the role of TMD in the treatment or prevention of amyotrophic lateral sclerosis, statin-induced skeletal muscle damage, diabetic cardiomyopathy, and diabetes-related peripheral arterial disease. The research methods used in these studies were briefly reviewed and the results were represented, which were consistent with the hypothesis or purpose of the study related to the role of TMD in treating the aforementioned diseases. In addition, the promising role of TMD in the treatment of COVID-19 was briefly discussed.

## Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease clinically characterized by the loss of upper and lower motor neurons, which has long been associated with metabolic dysfunction. Overall, these metabolic disturbances likely promote the use of fat as a primary energy source to protect against protein catabolism, which causes a depletion of energy reserves, loss of body fat mass and a decrease in body mass index [11]. Interest in targeting metabolic dysfunction as a therapeutic approach has only recently increased. In 2021, a study was conducted by Scaricamazza, et al. to evaluate the therapeutic potential of TMD in the $SOD1^{G93A}$ mouse model of ALS, where mice were treated orally with drinking water-soluble TMD at a dose of 20 mg/kg from the onset of disease. The effect of TMD on disease progressing was evaluated examining metabolic parameters, histological changes and grip strength in skeletal muscles, spinal cord, and peripheral nerves [12].

The study showed that oral administration of TMD at the onset of ALS improved muscle performance and energy metabolism, and increased survival in mice. Moreover, the study showed that TMD protects neuromuscular junctions (NMJs), preserves spinal motor neurons, and reduces neuroinflammation. These benefits of TMD can be attributed to improved mitochondrial function and ultimately ATP production. The ability of TMD to improve energy metabolism provides new evidence for a therapeutic approach to the treatment of ALS. The study provided evidence that TMD can, in addition to the metabolic effects, provide neuroprotection through other mechanisms.

Scaricamazza study results are consistent with the results of other studies, where it was observed that TMD protects against the dismantlement of NMJs, an event that typically occurs in the early phase of disease in $SOD1^{G93A}$ mice [13]. It has also been suggested that NMJ abnormalities predict degeneration of both distal axons and spinal motor neurons in $SOD1^{G93A}$ mice [14]. Thus, the beneficial effects of TMD may arise from a delay in NMJ disassembly, which is considered the initial event of the death phenomenon underlying motor neuron degeneration in ALS [15]. In this consistent, TMD exerted a protective effect on peripheral nerves of $SOD1^{G93A}$ mice, inhibiting the degeneration of Wallerian-like neurons and attenuating the loss of spinal motor neurons. The activation state of astrocytes and microglia in the spinal cord and the infiltration of CD68+ macrophages in the sciatic nerve, which were shown to be increased during the course of the disease in $SOD1^{G93A}$ mice, were attenuated by TMD treatment [16].

## Statin-Induced Skeletal Muscle Damage

Statins, as the main cholesterol-lowering drug in coronary heart disease, induce skeletal muscle injury and impair adaptation to exercise [17]. The proposed mechanism is dysfunction of energy metabolism [18]. Exercise rehabilitation has been shown to improve cardiorespiratory fitness parameters and exercise capacity in patients with coronary heart disease (CHD) [19]. In a study conducted by Song, et al. and published in 2018, the effect of TMD as a metabolic modulator on skeletal muscle energy metabolism and exercise intolerance associated with statins was investigated [20]. To get the aim of the study, a murine model of skeletal muscle injury induced by statin E knockout (ApoE-/-) was constructed, then it was clarified whether TMD could improve statin-associated exercise intolerance through modulation of skeletal muscle energy metabolism. High-fat fed apolipoprotein mice were randomly devided into five groups: sedentary, exercise, exercise + simvastatin, exercise + TMD, and exercise + simvastatin + TMD. The last three groups were trained for 8 weeks, in which exercise + simvastatin group and exercise + simvastatin + TMD group recieved gavage of 20mg/kg/day of simvastatin, while TMD was given by gavage at a dose of 30mg/kg/day to exercise +TMD group, and exercise + simvastatin + TMD group. Exercise capacity was assessed at the end of the treatment using forelimb grip strength, hanging grid test, and a running tolerance test. At the end of treatment, plasma glucose, creatine kinase, and lipid concentrations were measured. After sacrifice, gastrocnemius muscles were preserved to assess muscle morphology and fiber type. Energy metabolism was evaluated by plasma lactic acid concentration, ragged red fibers, and glycogen stores. To assess the mitochondrial function, mitochondrial complex III activity, membrane potential, and citrate synthase activity were measured. Oxidative stress was also assessed by superoxide dismutase activity, superoxide in mitochondria, and the redox state of glutathione.

It turned out that exercise training had no effect on lipid concentrations in high-fat fed ApoE-/- mice while decreased lipid concentrations and increased creatine kinase have been observed with additional treatment with simvastatin. Exercise training alone increased exercise capacity, but the addition of simvastatin caused this capacity to decrease. Likewise, muscle fiber cross-sectional area and the proportion of slow-twitch fibers increased in the exercise group but decreased in the simvastatin plus exercise group. In addition, simvastatin increased centronuclear fibers and caused an imbalance in energy metabolism by inhibiting complex III activity and thus promoting oxidative stress in the stomach. It was demonstrated in this study that TMD can reverse simvastatin-induced exercise intolerance and muscle damage, and that it was able to restore muscle fiber hypertrophy and facilitate the fast-to-slow transition. Also, TMD rescued energy metabolism dysfunction and gastric oxidative stress.

TMD induced recovery of the oxidative phenotype and increased fiber cross-sectional areas in response to training exercise leading to attenuation of statin-associated skeletal muscle injury. On the other hand, adaptation to exercise training was improved in high-fat-fed ApoE-/- mice. It should be noted that TMD showed its positive effects without any effect on the lipid-lowering properties of statins. Thus, TMD can be a suitable choice for treating unwanted exercise intolerance induced by statins during cardiac rehabilitation in patients with coronary heart disease.

## Trimetazidine for diabetics

### Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is attributed to multiple factors such as hyperglycemia, inflammation, and mainly oxidative stress [21]. It is a leading cause of death in patients with diabetes, representing a higher risk factor than non-diabetic patients for developing cardiomyopathy.

NADPH oxidase 2 (Nox2) induces oxidative stress by virtue of its catalytic activity in diabetic hearts, which ultimately leads to fibrosis [22]. Transient receptor potential channel 3 (TRPC3), along with Nox2, plays critical roles in cardiac remodeling. At present, there is no effective treatment strategy for DCM and its management represents a major challenge [23]. This creates an urgent need to develop new and more efficient therapeutic approaches for the clinical management of this disease. TMD, by modulating membrane homeostasis and counteracting metabolic disturbances, has been shown to be effective in preventing cardiac fibrosis and improving cardiac function in type 1 or type 2 diabetes-induced cardiomyopathy in rat models [24]. It has recently been suggested that TMD can be used for the prevention and treatment of DCM [25]. However, the underlying mechanism of the beneficial effects provided by TMD in the context of DCM is not yet known.

To examine whether TMD prevents cardiomyopathy induced by insulin-dependent type 1 diabetes, a study was performed by Tang, et al. In 2019 on Wistar rats, which were randomly divided into a control group (vehicle alone), a diabetes group, and diabetes, treated-with TMD, group. Diabetes was induced by injection a single dose (55 mg/kg) of streptozocin (STZ) prepared in 0.1 M sodium citrate buffer (pH = 4.5). STZ causes diabetes in mice through hyperglycemia, increased and decreased levels of advanced glycation end products (AGEs) and insulin, respectively. The control group was injected only with citrate buffer. Diabetic

rats were randomly divided into two groups: an untreated group and a TMD-treated diabetic group, which was treated with TMZ or vehicle for 11 weeks. Cardiac function, histology, plasma biochemistry and molecular mechanism were assessed. It was found that, diabetic rats were characterized by left ventricular dysfunction, cardiac hypertrophy, fibrosis, and signs of inflammation and oxidative stress in the myocardium, which were accompanied by elevated levels of NADPH oxidase 2 (Nox2) and transient receptor potential channel 3 (TRPC3) in the heart [26]. The study revealed that TMD:

Didn't affect development of diabetes in streptozocin-treated rats;

- Counteracted heart dysfunction caused by diabetes;
- Protected against left ventricular hypertrophy and fibrosis resulting from diabetes;
- Inhibited oxidative stress induced by hyperglycemia;
- Prevented the increase of Nox2 and TRPC3 in diabetic rats;
- Mitigated inflammation caused by oxidative stress.

In summary, TMD treatment improved diabetes-associated structural and functional alterations by inhibiting Nox2 and TRPC3 without having any effect on glucose, insulin, or AGEs levels. Based on the results of this study, it has been suggested that TMD could be used as a treatment for type 1 diabetes-associated cardiomyopathy [26].

## Peripheral Arterial Disease, Associated with Diabetes

Diabetes is a major risk factor for developing peripheral arterial disease (PAD) in the lower extremities, which has a widespread prevalence [27]. Not only that, but diabetes also accelerates the progression of the disease and increases its severity, resulting in more serious outcomes including amputation and mortality [28]. It has been found that among PAD patients with chronic limb ischemia, approximately 27% to 76% have diabetes [29]. Although open surgery and endovascular technology are currently considered as the first-line choices for revascularization of PAD, the clinical outcomes are highly dependent on the anatomical pattern of the disease [30]. Medical treatments that have direct benefits in reducing limb-related adverse events, improving quality of life, and enhancing performance status in advanced PAD are limited [31].

In 2021, Yang, et al. conducted a study aiming to evaluate the potential therapeutic effect of TMD on ischemic damage in db/db mice and to interpret the underlying mechanisms. Seven-week-old male db/db mice were fed a standard diet ad libitum with free access to drinking water. Fasting blood glucose levels were measured every three days. Mice with blood glucose levels above 16.7 mmol/L underwent left femoral artery ligation (FAL). After anesthesia, the femoral artery was isolated and ligated with 5-0 silk sutures at the distal and proximal locations (maintaining the same distance in all mice). After FAL, mice were divided into two group (n=10): TMD-treated group, which was given 10 mg/kg of TMD , and the saline group, which was given an equal volume of saline. TMD and saline were administered intragastrically every day for 2 weeks. In addition, the control group (n=10) underwent a sham operation, placing a suture under the femoral artery without ligation. Limb ischemia and limb function were assessed, and capillary density and muscle regeneration were measured in-vivo. Western blotting was used to confirm the expression of vascular endothelial growth factor (VEGF) and myogenic regulators, while ELISA analysis was used to measure serum intercellular adhesion molecule 1 (ICAM-1) levels. The study demonstrated that TMD treatment significantly attenuated foot injury in the ischemic hindlimb in diabetic mice and improved angiogenesis by regulating the expression of ICAM-1 and VEGF-A. Moreover, TMD might increase myogenic regulators and thus stimulate myogenesis [32]. Based on the result of this study, TMD is considered effective as a complementary non-surgical treatment for diabetic peripheral artery disease.

## Trimetazidine and COVID-19

Research has shown that about 20% of COVID-19 patients had signs of acute cardiac injury (ACI), measured by high-sensitivity troponin, and was associated with a fourfold increase in mortality [33]. Pharmacotherapy for ACI in COVID-19 is necessary to prevent cardiac fibrosis and heart failure. TMD may be effective in treating acute coronary syndrome and other ischemic events in COVID-19 because it is able to modulate cardiac fibroblast activity and the Akt/caspase-3 signaling pathway [34]. In addition, it, as an inhibitor of fatty acid oxidation, interferes with the penetration and replication of SARS-CoV-2 and may therefore attenuate the pathogenesis of SARS-CoV-2 infection [35]. TMD also has antioxidant and anti-inflammatory effects by inhibiting nuclear factor kappa B (NF-κB) activation and reactive oxygen species production, and it consequently exhibits cardioprotective effects by reducing mitochondrial dysfunction, oxidative stress, and apoptosis. Additionally, TMD stimulates nuclear factor erythroid-related 2 (Nrf2), a major transcription factor of the antioxidant pathway [36].

TMD therefore may be effective against ACI in COVID-19 by activating Nrf2 and suppressing the NF-κB signaling pathway, since ACI in COVID-19 is associated with induction of oxidative stress and activation of the NF-κB signaling pathway [37]. Moreover, TMD has immunomodulatory properties and reduces cardiac inflammation in heart failure by inhibiting the release of proinflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor

necrosis factor alpha (TNF-α). In brief, due to the anti-inflammatory and antioxidant effects of TMD, it can be proposed as an effective drug for the treatment of ACI in COVID-19 [38]. In the same context, it has been proposed that the use of TMD in combination with conventional therapy in patients admitted with a diagnosis of moderate to severe acute respiratory syndrome caused by SARS-CoV2 infection reduces the severity of acute myocardial injury compared with conventional therapy [39].

## Conclusion

Trimetazidine is an effective, well-tolerated drug for the treatment of angina and ischemic disorders. It is assumed that the main mechanism of action of trimetazidine is to improve energy utilization by cardiomyocytes and maintain sufficient energy supply during ischemia. However, as a non-specific metabolic modulator, trimetazidine was the subject of several studies aimed at examining its effectiveness in the treatment of various diseases associated with metabolic disorders, such as amyotrophic lateral sclerosis, cardiomyopathy or peripheral arterial disease, associated with diabetes. The results of these studies confirmed the effectiveness of trimetazidine in the treatment or prevention of the diseases studied.

## Conflict of Interest

The authors declare no conflict of interest.

## References

1. Tsioufis K, Andrikopoulos G, Manolis A (2015) Trimetazidine and cardio protection: facts and perspectives. Angiology 66(3): 204-210.

2. Cross HR (2001) Trimetazidine for stable angina pectoris. Expert Opin Pharmacother 2(5): 857-875.

3. Lee L, Horowitz J, Frenneaux M (2004) Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. Eur Heart J 25(8): 634-641.

4. Kantor PF, Lucien A, Kozak R, Lopaschuk GD (2000) The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacylcoenzyme a thiolase. Circ Res 86(5): 580-588.

5. Csaba AD (2016) Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. American Journal of Therapeutics 23: 871-879.

6. Kumar AA, Kelly DP, Chirinos JA (2019) Mitochondrial dysfunction in heart failure with preserved ejection fraction. Circulation 139(11): 1435-1450.

7. Ponikowski P, Lopatin YM, Rosano GM, Fragasso G, Lopaschuk GD, et al. (2016) Rationale and Benefits of Trimetazidine by Acting on Cardiac Metabolism in Heart Failure. Int J Cardio 15(203): 909-915.

8. Shu H, Peng Y, Hang W, Zhou N, Wang DW (2021) Trimetazidine in Heart Failure. Front Pharmacol 11: 569132.

9. Cross HR (2000) Trimetazidine: a novel protective role via maintenance of Na(+)/K(+)-ATPase activity. Cardiovasc Res 47(4): 637-639.

10. Wu L, Luan Y, Li Y, Wang M, He J, et al. (2020) Effects of trimetazidine on ventricular remodeling in coronary artery disease patients with left ventricular hypertrophy: the rationale and design of a randomized controlled trial. BMC Cardiovasc Disord 20(273): 7.

11. Wobst HJ, Mack KL, Brown DG, Brandon NJ, Shorter J (2020) The clinical trial landscape in amyotrophic lateral sclerosis-Past, present, and future. Medicinal Research Reviews 40: 1352-1384.

12. Scaricamazza S, Salvatori I, Amadio S, Nesci V, Torcinaro A, et al. (2021) Repurposing of Trimetazidine for amyotrophic lateral sclerosis: A study in SOD1G93A mice. British Journal of Pharmacology 179( 8): 1732-1752.

13. Dobrowolny G, Lepore E, Martini M, Barberi L, Nunn A, et al. (2018) Metabolic Changes Associated With Muscle Expression of SOD1 G93A. Front Physiol 9: 831.

14. Clark JA, Southam KA, Blizzard CA, King AE, Dickson TC (2016) Axonal degeneration, distal collateral branching and neuromuscular junctionarchitecture alterations occur prior to symptom onset in the SOD1G93A mousemodel of amyotrophic lateral sclerosis. Journal of Chemical Neuroanatomy 76(PtA): 35-47.

15. Bruneteau G, Bauché S, Aguilar JL, Brochier G, Mandjee N, et al. (2015) Endplate denervation correlates with Nogo-A muscle expression in amyotrophic lateral sclerosis patients. Annals of Clinicaland Translational Neurology 2(4): 362-372.

16. Chiot A, Zaidi S, Iltis C, Ribon M, Berriat F, et al. (2020) Modifying macrophages at the periphery has the capacity to change microglialreactivity and to extend ALS survival. Nature Neuroscience 23(11): 1339-1351.

17. Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, et al. (2013) Simvastatin impairs exercise training adaptations. J Am Coll Cardiol 62: 709-714.

18. Schirris TJ, Renkema GH, Ritschel T, Voermans NC, Bilos A, et al. (2015) Statin-induced myopathy is associated with mitochondrial complex III inhibition. Cell Metab 22: 399-407.

19. Lavie CJ, Milani RV (2011) Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention progress in cardiovascular diseases. Prog Cardiovasc Dis 53: 397-403.

20. Song M, Chen FF, Li YH, Zhang L, Wang F, et al. (2018) Trimetazidine restores the positive adaptation to exercise training by mitigating statin-induced skeletal muscle injury. J Cachexia Sarcopenia Muscle 9(1): 106-118.

21. Bugger H, Abel ED (2014) Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 57(4): 660-671.

22. Liu Y, Zhang J (2015) Nox2 contributes to cardiac fibrosis in diabetic cardiomyopathy in a transforming growth factor-β dependent manner. Int J Clin Exp Pathol 8(9): 10908-10914.

23. Kitajima N, Tomita NT, Watanabe M, Kuwahara K, Sato Y, et al. (2016) TRPC3 positively regulates reactive oxygen species driving maladaptive cardiac remodeling. Sci Rep 6: 37001.

24. Zhang L, Ding WY, Wang ZH, Tang MX, Wang F, et al. (2016) Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. J Transl Med 14(1): 109.

25. Zhang L, Ding WY, Wang ZH, Tang MX, Wang F, et al. (2011) Early administration of trimetazidine may prevent or ameliorate diabetic cardiomyopathy. Med Hypotheses 76(2): 181-183.

26. Tang SG, Liu XY, Wang SP, Wang HH, Jovanović A, et al. (2019) Trimetazidine prevents diabetic cardiomyopathy by inhibiting Nox2/TRPC3-induced oxidative stress. J Pharmacol Sci 139(4): 311-318.

27. Gogalniceanu P, Lancaster RT, Patel VI (2018) Clinical assessment of peripheral arterial disease of the lower limbs. N Engl J Med 378(18): e24.

28. Criqui MH, Aboyans V (2015) Epidemiology of peripheral artery disease. Circ Res 116(9): 1509-1526.

29. Dick F, Diehm N, Galimanis A, Hussman M, Schmidli J, et al. (2007) Surgical or endo vascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 45(4): 751-761.

30. Hiramoto JS, Teraa M, Borst GJ, Conte MS (2018) Interventions for lower extremity peripheral artery disease. Nat Rev Cardiol 15(6): 332-350.

31. Olin JW, White CJ, Armstrong EJ, Dodov D, Hiatt WR (2016) Peripheral artery disease: evolving role of exercise, medical ther apy, and endovascular options. J Am Coll Cardiol 67(11): 1338-1357.

32. Yang Y, Xu Q, Li T, Shao S (2021) Trimetazidine ameliorates hindlimb ischaemic damage in type 2 diabetic mice. Ann Med 53(1): 1099-1107.

33. Onohuean H, Al-Kuraishy HM, Al-Gareeb AI, Qusti S, Alshammari EM, et al. (2021) Covid-19 and development of heart failure: mystery and truth. Naunyn Schmiedebergs Arch Pharmacol 394(10): 2013-2021.

34. Huang Q, Deng X, Li Y, Sun X, Chen Q, et al. (2020) Clinical characteristics and drug therapies in patients with the commontype coronavirus disease 2019 in Hunan, China. Int J Clin Pharm 42(3): 837-845.

35. Salinas P, Travieso A, Vergara-Uzcategui C, Tirado-Conte G, Macaya F, et al. (2021) Clinical profle and 30-day mortality of invasively managed patients with suspected acute coronary syndrome during the COVID-19 outbreak. Int Heart J 62(2): 274-281.

36. Williams CG, Jureka AS, Silvas JA, Nicolini AM, Chvatal SA, et al. (2021) Inhibitors of VPS34 and fatty-acid metabolism suppress SARS-CoV-2 replication. Cell Rep 36(5): 109479.

37. Zhang H, Liu M, Zhang Y, Li X (2019) Trimetazidine attenuates exhaustive exercise-induced myocardial injury in rats via regulation of the Nrf2/NF-κB signaling pathway. Front Pharmacol 10: 175.

38. Al-kuraishy H, Al-Gareeb AI, Welson NN, Batiha G (2022) Trimetazidine and COVID-19-induced acute cardiac injury: a missed key. International Journal of Clinical Pharmacy 44: 832-833.

39. Knowlton KU (2020) Pathogenesis of SARS-CoV-2 induced cardiac injury from the perspective of the virus. J Mol Cell Cardiol 147: 12-17.