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Review Article

Immunomodulatory and antioxidant effects of pentoxifylline and other therapeutic agents in the management of myocardial injury

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ABSTRACT

Myocardial injury, particularly during myocardial infarction (MI), triggers an inflammatory response that is crucial for starting the myocardial healing process but is also responsible for cardiac remodeling and heart failure that can develop in as much as a quarter of the patients post-MI. Pentoxifylline (PTX) is a drug with potential cardiovascular benefits due to its anti-inflammatory and antioxidant properties. The aim of this review is to highlight the immunomodulatory and antioxidant effects of PTX in the management of myocardial injury. A search strategy was designed using medical subject headings (MeSH) terms of antioxidant effect, immunomodulatory, myocardial injury, and PTX for search on PubMed, and MEDLINE databases. PTX has been studied for its potential therapeutic effects in managing myocardial injury. It was extensively investigated in vivo as well as in human clinical trials and has provided promising results. Some of the promising findings include an anti-inflammatory and antioxidant effect with some beneficial clinical outcomes. These findings were evident as decreased levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and certain interleukins such as IL-1, decreased oxidative stress markers such as malondialdehyde (MDA) while increasing antioxidants such as glutathione, improved ejection fraction in some patients and improved mortality profile in one meta-analysis. In conclusion**,** it can be concluded that PTX has potential immunomodulatory and antioxidant effects in the management of myocardial injury.

Keywords: *Immunomodulation; Inflammation; myocardial infarction; oxidative stress; myocardial injury; pentoxifylline.*

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1. Introduction

Myocardial infarction (MI) is a significant cardiovascular ailment that has the potential to result in mortality **[1]**. MI results in cardiomyocyte death in the affected area caused by prolonged ischemia with subsequent cardiac remodeling potentially leading to ventricular dysfunction and heart failure **[2, 3]**.

According to its etiology, MI can be a spontaneous MI brought about by atherosclerosis-related coronary incidents known as type 1, MI due to diminished oxygen supply or heightened oxygen demand to the myocardium known as type 2, or MI with sudden cardiac death in the case of unavailable cardiac biomarker results known as type 3. The majority of ST-elevation myocardial infarction (STEMI) patients in addition to many Non-ST-Elevation Myocardial Infarction patients (NSTEMI) fit into type 1 MI **[4]**. In addition to the clinical presentation which could range from asymptomatic patients to patients with cardiac

arrest or cardiogenic shock, there are various means which aid in MI diagnosis **[5]**. The electrocardiogram's depiction of the presence of Q waves or alterations in the ST-segment or T segments is a mainstay of diagnosis, in addition to the detection of the cardiac biomarkers released by damaged cardiomyocytes like high-sensitivity cardiac troponin and creatine kinase-MB **[6]**.

The immune system is constantly in communication with the heart through messengers such as cytokines, hormones, and neurotransmitters **[7]**. The immune system plays an important role in the repair and remodeling of heart tissue post-MI. The non-specific innate immunity including macrophages, neutrophils, and mast cells as well as the adaptive immunity including T and B cells can all be involved in cardiac injury and repair mechanisms **[8, 9]**. However, a continued immune response produces negative outcomes of pathological ventricular remodeling **[10]**.

The search continues for therapies that help regulate the balance between the pro-inflammatory and the anti-inflammatory processes post-MI to minimize cardiac remodeling that can lead to worse patient outcomes **[11]**.

Reactive Oxygen Species (ROS), at their minimal physiological concentration, act as second messengers for important intracellular signals. Oxidative stress is the state of having higher ROS levels than the antioxidant system can clear **[12]**. The nuclear transcription factor kappa B (NF-κB) is triggered through increased ROS concentrations which results in the transcription of many proinflammatory cytokines and adhesion molecules. Thus, oxidative stress plays a role in the production of cytokines linking it to inflammation and endothelial dysfunction **[12, 13]**. Oxidative stress is considered to be a risk factor for coronary artery disease (CAD) development, progression, and prognosis **[13]**. Evidence suggests that oxidative stress plays a role in the cardiac remodeling process following MI with some in-vitro studies confirming the reduction of left ventricular remodeling with the use of certain antioxidants **[14]**.

Pentoxifylline (PTX) is a methylxanthine derivative with vasoactive properties that enhance hemodynamic characteristics through the reduction of blood viscosity. It is approved by the Food and Drug Administration (FDA) at a dose of 400mg three times daily for the management of intermittent claudication which is commonly apparent with chronic lower limb occlusive peripheral vascular disease **[15]**. More than 50 years of safety data support the generally safe and tolerable use of PTX. The most encountered side effects are gastrointestinal such as nausea, vomiting, or dyspepsia with a lower incidence of headache and dizziness **[16-18]**. Incidences of bleeding with or without increased prothrombin time have been reported, however, no causal relationship with PTX could be established **[19]**. In addition, the safe use of PTX in MI patients was concluded in two different trials with only a few patients suffering from nausea and headaches with no discontinuation required **[20, 21]**.

2. Methods

In the present review, different study designs like clinical trials, systematic reviews, and narrative reviews were included. A search strategy was designed using medical subject headings (MeSH). The MeSH terms of antioxidant effect, immunomodulatory, myocardial injury, and pentoxifylline were used to search PubMed, and MEDLINE databases as shown in **Fig.1.**

Studies in the English language and all relevant updated publications up to November 2023 were included. Our inclusion criteria

primarily focused on the latest published literature that focuses on the immunomodulatory and antioxidant effects of PTX in the management of myocardial injury with trials before the year 2000 or studies having less than 10 patients excluded as shown in **Table 1**.

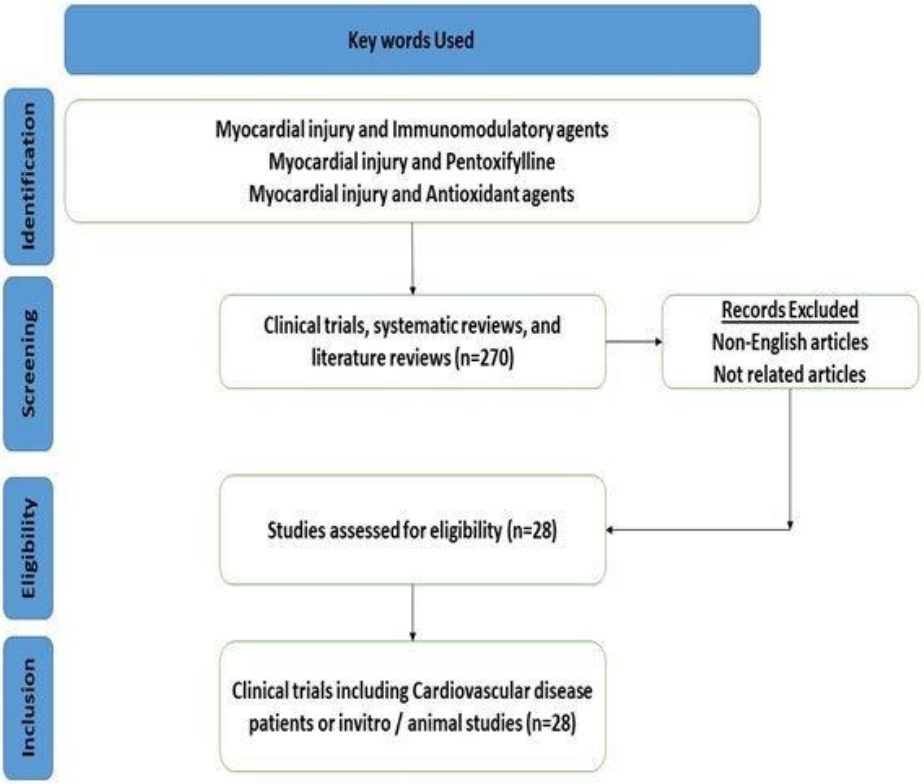

Fig. 1. Search strategy Flow chart

Table 1. Inclusion criteria for search strategy

Parameter	Criterion
Trials and studies	Clinical trials including cardiovascular patients or in-vitro / animal studies
Intervention	Immunomodulators, pentoxifylline.
Comparator	Other therapeutic interventions, or placebo group.
Outcome	Inflammatory markers in plasma Left ventricular Ejection fraction Mortality rates
Setting	All settings

3. Results and discussion

3.1. The Role of Immunity and Inflammation in Myocardial Infarction

The release of damage-associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1), heat shock protein (HSP), and low molecular weight hyaluronic acid from necrotic myocardial cells results in the induction of numerous inflammatory cytokines. This is what initially drives the innate immune system into action as immune cells such as neutrophils, monocytes, and dendritic cells all start to reach the affected tissue **[22]**. Increased oxidative stress as a result of overwhelmed antioxidant mechanisms after MI also contributes to upregulating the inflammatory signal **[23]**.

Neutrophils are the first to be recruited to the infarcted area which adhere to endothelial cells and penetrate the tissue through the assistance of adhesion molecules such as selectins, integrins, vascular cell adhesion molecule-1 (VCAM-1) and Intercellular adhesion molecule-1 (ICAM-1) **[24]**. Neutrophils can be polarized into N1 which produces pro-inflammatory cytokines such as interleukin (IL)-12a and IL-1β while N2 can produce anti-inflammatory cytokines such as IL-10 **[22]**.

Monocytes are recruited to the infarcted myocardium without entering the tissue. In the inflammatory phase, the pro-inflammatory monocytes dominate and differentiate in the pro-inflammatory macrophage M1. M1 macrophages penetrate the tissue and contribute to inflammation through the release of pro-inflammatory cytokines such as IL-1 and IL-12. With time the reparative stage ensues where monocytes predominate and differentiate into M2 macrophages which release anti-inflammatory and reparative proteins such as IL-10, vascular endothelial growth factor (VEGF) and transforming growth factor beta 1(TGF-β1). M2 macrophages act to limit the inflammatory process and mediate angiogenesis and myofibroblast growth **[9, 22]**.

The repair phase of myocardial injury involves the infiltration of numerous T and B lymphocytes into the affected tissue **[25]**. Regulatory T-cells produce cytokines that favor macrophage polarization into M2 to promote cardiac healing while activated CD8+ T cells produce granzyme B which contributes to cell death and negative cardiac tissue remodeling **[26]**. **Fig. 2**. Shows the Role of Immune cells in Myocardial Infarction

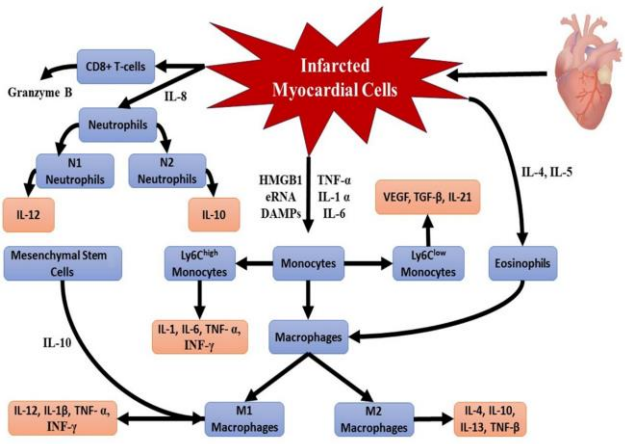

Fig. 2. Role of Immune Cells in Myocardial Infarction

3.2. The Role of Oxidative Stress in Myocardial Infarction

ROS in the heart mainly arise via the mitochondrial electron transport chain, xanthine oxidase, NADPH oxidases, and nitric oxide synthases. Example of ROS includes superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) **[27]**.

Superoxide anions can give rise to either peroxynitrite (ONOO-) or hydrogen peroxide. Additionally, they can be involved in a reaction with hydrogen peroxide to produce a hydroxyl radical **[28]**. Peroxynitrite itself can be converted to peroxynitrous acid (ONOOH) with protonation. Hydrogen peroxide can give rise to hydroxyl radical when it undergoes a Fenton reaction or to hypochlorous acid (HOCl) via myeloperoxidase activity with hypochlorous acid (HOCl) itself reacting with hydrogen peroxide to form dioxygen ($^1O_2$) **[29]**. **Fig. 3.** Shows reactive oxygen species formation and detoxification.

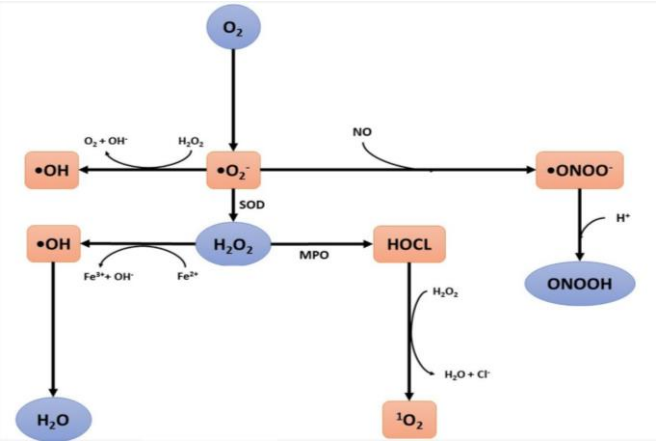

Fig. 3. Reactive oxygen species formation and detoxification

The contribution of oxidative stress to cardiovascular diseases is evident through the finding that antioxidants improved endothelial function in CAD patients in some studies **[30]**. It was observed that patients with merely cardiovascular risk factors such as hyperlipidemia and smoking as well as CAD patients all exhibit high oxidative stress **[13]**. At the level of MI, revascularized STEMI patients who had a major cardiac event later had high levels of oxidative stress markers **[31]**.

ROS are also implicated in the generation of oxidized LDL which accumulates sub-endothelially and starts a reaction of inflammation and endothelial dysfunction initiating atherosclerosis. ROS are implicated in atherosclerosis and CVD as well as hypertension, diabetes, cardiac hypertrophy, and heart failure **[32]**.

Besides inflammation, ROS also play a role in the triggering of cardiac remodeling after MI. ROS can signal the development of cardiac hypertrophy, activate extracellular matrix remodeling via activation of matrix metalloproteases (MMPs), and can also trigger cardiomyocyte apoptosis **[33]**.

In normal circumstances, the low levels of ROS produced are equivalent to their removal **[28]**. The phenomenon known as redox signaling, which refers to the specific and reversible oxidation-reduction alterations of components involved in cellular signaling has now been recognized to be involved in both physiological and disease processes. In the heart, these

modifications can regulate gene expression, excitation-contraction coupling, as well as processes like cell growth, migration, differentiation, and death **[34]**.

3.3. Pharmacology of pentoxifylline

PTX has been utilized in several disease areas. Beyond its FDA-approved indication, PTX is used off-label in diseases such as severe alcoholic liver disease, non-alcoholic fatty liver disease, peripartum, idiopathic and ischemic cardiomyopathy, and chronic kidney disease **[35, 36]**. PTX is also employed off-label for the treatment of venous ulcers. A comprehensive literature review conducted by the Cochrane Collaboration revealed that PTX is an efficacious intervention for venous ulcers, regardless of whether compression therapy is administered or not **[37]**.

The hemorheological effects of PTX and its metabolites contribute to a decrease in blood viscosity, thereby augmenting blood flow and peripheral tissue oxygenation. The specific molecular effects through which PTX exerts its pharmacological action are not fully clear. Nevertheless, multiple pathways are hypothesized to be involved **[15]**. Those hypotheses suggest a role for PTX as an immune modulator, anti-TNF-α agent, and hemorheological modulator in addition to affecting the adhesion molecules **[38]**.

Normally, cyclic adenosine monophosphate (cAMP) in platelets modulates the cyclo-oxygenase enzyme that synthesizes prostaglandins G_1 and H_2 which form thromboxane A2 and thus lead to increased platelet aggregation. As PTX causes the level of cAMP to increase by action of phosphodiesterase (PDE) inhibition, this leads to less activation of cyclo-oxygenase enzyme and thus ultimately less platelet aggregation. Also, PTX raises the prostacyclin level which activates adenylyl cyclase which results in higher cAMP and platelet aggregation inhibition **[39]**. PTX also acts to increase plasminogen activator and plasmin while at the same time decreasing fibrinogen thus further enhancing blood viscosity **[38]**.

3.4. Pentoxifylline: Anti-inflammatory and Immunomodulatory Effects

Immunomodulation can take the form of general modulation of more than one inflammatory pathway as with PTX or specific targeting of a certain cytokine or cellular pathway of inflammation as with biologics like canakinumab, etanercept, or anakinra **[40]**.

PTX possesses immunomodulatory properties that enhance white blood cell (WBC) deformability while simultaneously decreasing neutrophil degranulation, reducing leukocyte adhesion, and decreasing the sensitivity of leukocytes to cytokines **[39]**.

The most common hypothesized mechanism for PTX is the non-selective inhibition of the PDE enzyme. In particular, the inhibition of the isoenzyme PDE-4 is crucial as it is highly expressed in inflammatory cells such as neutrophils, macrophages, T cells, and endothelial cells **[41]**. PDE inhibition leads to elevated levels of cAMP and increased protein kinase A activity and that subsequently results in downregulation of the I kappa B kinase/Nuclear Factor-kappa B (IKK/NF-kB)-mediated transcription of pro-inflammatory cytokines such as TNF-α **[17]**.

The anti-inflammatory effect exerted by PTX is not only due to the inhibition of TNF-α but also due to decreasing the secretion of other inflammatory cytokines such as IL-1 and IL-6 and limiting the expression of adhesion molecules such as VCAM-1 and ICAM-1 **[17]**. PTX has also been observed to inhibit B lymphocytes and T lymphocytes and inhibit

neutrophil activation **[18]**.

A meta-analysis demonstrated that treatment with PTX significantly decreased the concentrations of TNF- α and C-reactive protein (CRP) in plasma. However, no significant change in plasma IL-6 concentrations was observed following PTX therapy **[42]**. In the study by Fernandes et. al., treating NSTEMI patients with PTX resulted in a significant reduction of CRP and TNF-α levels **[20]**. PTX has exhibited a positive effect on inflammation in other trials as well **[43, 44]**. CAD patients who were administered PTX for 2 months experienced a significant decrease in the levels of sVCAM-1 as a marker of endothelial dysfunction relating to inflammation **[45]**.

The use of PTX in ischemic cardiomyopathy patients resulted in a reduction in plasma concentrations of inflammatory markers TNF- α and CRP and led to an improved left ventricular ejection fraction **[46]**. When PTX use was investigated in type 2 diabetes mellitus patients, it was concluded that PTX resulted in TNF-α reduction in patients on angiotensin II receptor blocker (ARB) therapy and residual proteinuria **[47]**.

3.5. Pentoxifylline: Antioxidant Effects

The proposed antioxidant effects of PTX may be attributed to its suppression of neutrophil activation and thus decreased level of neutrophil-derived superoxide anions **[48]**. It is also reported that PTX can limit the production of other ROS like hydroxyl and superoxide anions by inhibiting xanthine oxidase **[49]**.

In a study of the antioxidant effects of PTX in mice with arsenic-induced cardiac oxidative damage, PTX was found to augment the activity of antioxidant systems such as superoxide dismutase, catalase, and glutathione peroxidase **[50]**. Using PTX in hypertensive diabetic patients resulted in a significant 20.2% reduction in the level of the oxidative stress marker malondialdehyde in the PTX group which did not occur in the control group **[51]**. In another study, diabetic patients treated with PTX had significantly decreased levels of thiobarbituric reactive substances (TBARS) which is a marker indicative of lipid peroxidation and oxidative stress **[52]**.

3.6. Effect of Pentoxifylline in Improving Myocardial Injury

In a study on NSTEMI patients where PTX was administered for 6 months, PTX-treated patients exhibited better outcomes concerning the endpoint of death, reinfarction, or rehospitalization **[20]**. On the contrary, a trial that investigated PTX in 98 STEMI patients who underwent thrombolytic therapy did not conclude a significant improvement in the development of 30-day major adverse cardiac events (MACEs). However, a significant improvement in troponin I concentration was observed in the PTX group when compared to placebo **[53]**. A more recent study that used PTX on 419 NSTEMI patients in the FDA-approved dose also failed to observe an improvement in the 1-year total MACEs of cardiovascular death, reinfarction, and rehospitalization but there was a significantly decreased risk for the need for coronary revascularization in the PTX arm **[21]**.

In patients suffering heart failure secondary to ischemia, the addition of PTX to standard treatment led to the clinical improvement of patients and enhanced ejection fractions in addition to improving some of the biomarkers of inflammatory, prognostic, and apoptotic profiles **[46]**. The use of PTX in severe heart failure patients in addition to guideline-directed medical therapy reduced the levels of TNF-α as a marker of inflammation and Fas/Apo-1 as a marker of apoptosis when compared to the control group at 1 month of treatment. This could imply the potential usefulness of PTX in heart failure

patients of severe classification **[54]**. In a meta-analysis consisting of six controlled trials involving 221 patients with cardiomyopathy and heart failure with left ventricular ejection fraction (LVEF) ≤ 40% that administered PTX, the use of PTX was associated with almost a fourfold decrease in all-cause mortality compared to control even though the individual studies examined concluded no such effect **[55]**.

Regarding in-vivo trials, PTX exhibited a potent cardioprotective effect when used to combat Adriamycin-induced cardiotoxicity in rabbits. The conferred benefits in the previous trial included lowering the levels of cardiac biomarkers such as creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH), oxidative stress markers such as MDA and glutathione as well as inflammatory markers TNF-α and IL-6 **[56]**. Furthermore, PTX when combined with vanillin and used in rats with isoproterenol-induced cardiac injury had resulted in the amelioration of the cardiac abnormalities evident as decreased oxidative stress marker MDA, and increased glutathione, decreased inflammatory markers TNF-α, IL-6, and IL-1β **[57]**.

3.7. Repurposed Anti-inflammatory and Immunosuppressive Agents

A comprehensive examination of clinical trials involving pharmacological interventions aimed at the immune system to improve MI or improve its prognosis is provided in **Table 2** and **Table 3**. These interventions range from general immunosuppressive therapy to more specific approaches that target defined pathways and factors.

The measured outcomes in those trials ranged between clinical outcomes as well as serum biomarkers or investigation-related outcomes. These outcomes include angiography-investigated restenosis, maximal oxygen uptake, respiratory quotient and exercise time upon exercise testing, New York Heart Association (NYHA) class, MACEs, cardiac magnetic resonance (CMR)-determined myocardial salvage, CMR-assessed infarct size, radionuclide ventriculography, echocardiographic studies including LVEF, left ventricular end-diastolic and end-systolic lengths, endothelium-dependent and endothelium-independent forearm blood flow by venous occlusion plethysmography. Also, serum biomarkers such as TNF-α, TGF-β, IL-6, IL-10, NT-pro-BNP, Fas/Apo-1, albuminuria, fibrinogen, leukocytic count, count of neutrophils, basophils, monocytes and lymphocytes, MDA, glycated hemoglobin, lipid profile, troponin, creatine kinase, von Willebrand Factor (vWF) and flow cytometric measures of platelet activation. However, the outcomes mentioned below are the ones that showed significance only.

Table 2. Clinical trials involving pentoxifylline for the treatment of myocardial injury

Reference	Design	*n*	Clinical Condition	Intervention	Dose/Administration	Follow-up	Outcomes
[58]	Randomized, double-blind, placebo-controlled	47	ischemic, hypertensive, or idiopathic-dilated cardiomyopathy and LVEF ≤ 40%	Pentoxifylline	600 mg twice daily	6 months	Neutral effect on LVEF
[46]	Randomized,	38	Ischemic	Pentoxifylline	400 mg three times daily	6 months	Improved NYHA

	double-blind, placebo-controlled		cardiomyopathy				class, LVEF, and reduced CRP NT-pro BNP, TNF-α and Fas/Apo-1
[54]	Randomized, double-blind, placebo-controlled	18	Idiopathic-dilated cardiomyopathy and advanced heart failure	Pentoxifylline	400 mg three times daily	1 month	Reduced TNF-α and Fas/Apo-1, and an increased LVEF
[59]	Randomized, double-blind, placebo-controlled	39	Idiopathic dilated cardiomyopathy	Pentoxifylline	400 mg three times daily	6 months	significant improvement in symptoms and left ventricular function.
[20]	Randomized, double-blind, placebo-controlled	64	NSTEMI patients	Pentoxifylline	400 mg three times daily	6 months	Significant reduction in CRP, TNF-α, and attenuation of decline in IL-10. Improves MACEs in the PTX group.
	Randomized	30	Patients requiring coronary artery bypass graft (CABG) for the first time	Pentoxifylline	600mg/day or 900mg/day for 5 days	Up to 1 day postoperative	Decreased IL-6 and respiratory index after cardiopulmonary bypass
[53]	Randomized, unknown blinding status	98	Anterior STEMI undergoing thrombolytic therapy	Pentoxifylline	One 1200 mg dose immediately before thrombolytic therapy	1 month	Significant lowering of troponin I in the PTX group
[21]	Randomized, single-blind, placebo-controlled	419	NSTEMI patients	Pentoxifylline	400 mg three times daily	20 months	Decreased risk of coronary revascularization

Table 3. Clinical trials including different repurposed therapeutic agents for the treatment of myocardial injury

Reference	Design	*n*	Clinical Condition	Intervention	Dose/Administration	Follow-up	Outcomes
[60]	Randomized, double-blind, placebo-controlled	112	STEMI patients undergoing percutaneous coronary intervention (PCI)	N-acetylcysteine (NAC)	20 mg/min for the first hour then 10 mg/min for 47 h	3 months	Reduced infarct size

[61]	Randomized, blinding unknown, placebo-controlled	30	Acute anterior MI	NAC	100 mg/kg IV (50 mg/kg IV bolus; 50 mg/kg infusion over 30 min)	2 weeks	Reduced infarct size and improved LVEF
[62]	Randomized, double-blind, placebo-controlled	22	Acute MI	NAC	15 g IV infused over 24 h	3 months	significant decrease in oxidative stress (MDA) and improved left ventricular function
[63]	Randomized, double-blind, placebo-controlled	11,484	Percutaneous coronary intervention	Tranilast	300 mg OR 450 mg twice daily oral for 1 month OR 3 months	9 months	No improvement regarding restenosis or mortality
[64]	Randomized, double-blind, placebo-controlled	288	Angina or old MI with denovo or restenotic lesion has undergone successful percutaneous transluminal coronary angioplasty (PTCA)	Tranilast	600 mg daily oral for 3 months	3 months	reduced restenosis rate
[65]	Randomized, placebo-controlled	60	ST-elevation myocardial infarction	Famotidine	40 mg daily	1 month	Reduced N-terminal pro-brain Natriuretic Peptide (Nt-proBNP), reduced left ventricular dilation, and improved LVEF
[66]	Randomized, open-label	50	Symptomatic congestive heart failure	Famotidine	30 mg daily for 6 months	6 months	Famotidine improved NYHA class, BNP level and reduced rehospitalization risk
[67]	Randomized, double-blind, placebo-controlled, 4-way crossover	12	Males with Chronic heart failure (NYHA II and III)	Cimetidine, famotidine, ranitidine	400 mg cimetidine twice daily, 40 mg famotidine daily, and 150 mg daily ranitidine for 7 days each with a 7-day washout period	7 days	No significant effect on left ventricular systolic function, aerobic metabolic performance, or exercise capacity
[68]	Randomized, double-	10,061	Previous myocardial infarction and high	Canakinumab	50 OR 150 OR 300 mg subcutaneously every 3	48 months	The 150 mg dose showed a lower rate

	blind, placebo-controlled		sensitivity CRP ≥ 2mg		months		of cardiovascular events independent of lipid-lowering
[69]	Randomized, double-blind, placebo-controlled	30	Acute Decompensated Heart failure and CRP ≥ 5mg	Anakinra	100 mg twice daily for 3 days then once daily for 11 days	2 weeks	Reduced CRP and IL-6
[70]	Randomized, double-blind, placebo-controlled	155	Non-ST-elevation acute coronary syndrome	Anakinra	100 mg subcutaneous daily for 2 weeks	1 year	Inflammatory markers such as IL-6 and hs-CRP were reduced
[71]	Randomized, double-blind, placebo-controlled	10	STEMI	Anakinra	100 mg subcutaneous daily for 2 weeks	2 weeks	Less cardiac remodeling evident as a reduced left ventricular end-systolic volume index
[72]	Randomized, double-blind, placebo-controlled	117	NSTEMI	Tocilizumab	280 mg IV once	6 months	Reduced CRP and high-sensitivity cardiac troponin
[73]	Randomized, double-blind, placebo-controlled	26	Acute MI	Etanercept	10 mg IV infusion	24 h	Reduced inflammation but increased platelet activation
[74]	Randomized, double-blind, placebo-controlled	47	Heart failure NYHA class III or IV	Etanercept	5 mg/m^2 OR 12 mg/m^2 subcutaneous biweekly for 3 months	3 months	Improved LVEF, LV end-systolic volume, and LV mass.
[75]	Open-label	18	Heart failure NYHA class III	Etanercept	25 mg subcutaneous single dose	7 days	Improved forearm blood flow response in systemic endothelial vasodilator capacity

Conclusion

It can hence be concluded that PTX offers potential immunomodulatory and antioxidant effects in the management of myocardial injury. PTX can modulate the immune response that

starts to occur early post-MI and promote the repair of MI by promoting the formation of granulation tissue and eliminating dead myocardial cells. Moreover, the hemodynamic circulation enhancement effect through the reduction of blood viscosity makes PTX a potential candidate among other repurposed immunomodulatory agents in the management of myocardial injury.

Recommendation

Further large center controlled trials are encouraged to fully elucidate and outline the effects of PTX on different myocardial injury types as well as determine the best duration of use to obtain the desired effect.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Ethics approval and consent to participate

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in the main manuscripts of the referenced articles.

Competing interests

The authors have no financial or non-financial competing interests to declare.

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Author contribution

Asmaa Saeed: review the idea and outline, Write the original draft and manuscript revision. Nagwa Ali Sabri: editing, Supervision. Marwa Adel Ahmed: editing, Supervision. Mohamed Ayman Saleh: editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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