Review

MPO and Its Role in Cancer, Cardiovascular and Neurological Disorders: An Update

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MPO and Its Role in Cancer, Cardiovascular and Neurological Disorders: An Update

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Abstract: Myeloperoxidase (MPO) is an enzyme that contains a heme group, found mostly in neutrophils and in small amounts in monocytes and plays a major role in their anti-microbial activity. However, excessive levels of MPO have been linked to various disorders and identified as a major cause of tissue destruction. Inhibiting its activity can reduce the severity and extent of tissue damage. Over activity of MPO during chronic inflammation has been shown to be involved in tumorigenesis by inducing a hyper-mutagenic environment through oxidant interaction with DNA, causing DNA modification. Vascular endothelium is one of the most important targets of MPO and high levels have been associated with increased rates of cardiomyopathy, ischemic stroke, heart failure, myocardial infarction, and atrial fibrillation. Therefore, it may be considered a therapeutic target in the treatment of cardiovascular disorders. MPO also participates in the pathogenesis of neurodegenerative diseases. For example, an increase in MPO levels has been observed in the brain tissue of patients with Alzheimer's, Multiple sclerosis (MS), and Parkinson's diseases. In Alzheimer's disease, active MPO is mostly found in the location of beta amyloids and microglia. Therefore, targeting MPO may be a potential treatment and prevention strategy for neurological disorders. This review will discuss MPO's physiological and pathological role in cancer, cardiovascular, and neurological disorders.

Keywords: MPO; cardiovascular diseases; cancer; neurological disorders

Introduction:

Neutrophils

Neutrophils, which are one of the shortest-lived cells of mammals, are the most prevalent leukocyte population in the circulation. These cells are among cells with terminal differentiation and limited transcriptional activity continuously produced by the bone marrow[1,2]. Despite their short life, neutrophils play multiple roles in the immunogenic and inflammatory processes of the body. In addition to being one of the first lines of defense against various infections, due to having active oxygen species and numerous enzymes, they can destroy the pathogen as soon as the microbial species enters. Among other unique actions of neutrophils, the protrusion of their genomic DNA in the form of a neutrophil extracellular trap (NET) can be mentioned. Materials related to NETs are usually rich in nuclear histones due to their production from the nucleus and also, various types of granular proteins, cytosolic proteins, and most importantly antimicrobial proteins such as MPO can be observed in their structure. Of course, considering that the general composition of NETs can change depending on the type of stimulus, in some cases, they may originate from mitochondria, in which case they will lack histones. NETs are released to decrease the level of diffusion of pathogenic microorganisms and also help to destroy them. But, the point is that, in the case of unprogrammed immune responses, usually the irregular production of NETs can occur which leads to inflammation increment and damage of host cells. Neutrophils use different methods to play their role in

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inflammation and immunogenesis, the most important of which are enzymatic processes including the production of reactive oxygen species by nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, secretion of granule-derived MPO, and hydrolytic enzyme production[1,3,4].Indeed, neutrophils are multifunctional cells that have broad capabilities in a wide range of infectious and non-infectious disease conditions.

Myeloperoxidase (MPO)

MPO is a peroxidase enzyme containing a heme group, which is found in neutrophils and small amounts in monocytes. In early studies, MPO was proved to be an oxygen-dependent antimicrobial system in phagocytes, especially neutrophils [3,5,6]. During the process of myelopoiesis within the bone marrow, there is an active synthesis of myeloperoxidase in promyelocytes and promonocytes. However, in myeloid cells that have reached full differentiation, the synthesis of MPO typically ceases [7]. Neutrophils have 3 types of granules, the second and third types are free of peroxidase despite having different proteins but the granules of the first type are peroxidase positive due to the high amount of MPO, although these granules also contain many proteolytic enzymes that bind to the negatively charged proteoglycans inside the granules and according to the acidic pH inside the granules, these enzymes remain inactive[7,8].

The biosynthesis of MPO includes very complex processes during which after the production of pre-MPO as the first translation product in endoplasmic reticulum, glycosylation of six asparagine causes its conversion to inactive apo-pro-MPO, which is converted to active pro-MPO by adding heme. Then, in the secretory pathway from the endoplasmic reticulum, proteolytic processes and dimerization take place and cause the appearance of mature MPO, which is observed in neutrophilic granules (Figure 2)[9]. MPO, as an important part of NETs, is always present in cases where neutrophils flow to the site of inflammation to phagocytose pathogenic microorganisms, and by creating an alkaline environment inside the phagosome, it creates a stable environment for killing germs. Also, after the completion of the phagocytosis process, MPO with its peroxidation function helps to protect the surrounding tissues against substances caused by proteolysis[10]. Duo to prominent role of MPO in several disorders, its measurement method has a vital importance. Common protocol of measuring is spectrophotometric method which is so functional and helpful. Spectrophotometric assay is based on the oxidizing activity of o-diazinidine in an H2o2 rich environment which is a simple, low cost and sensitive method[11,12]. However, recently, a novel fluorometric method has been introduced. This colorimetric technique measures MPO activity specifically and is related to H2O2-dependant oxidation process of Thiamin. Distinctive feature of this protocol is an exceptional sensitivity, accuracy and specificity that makes it a dependable method in future studies[13].

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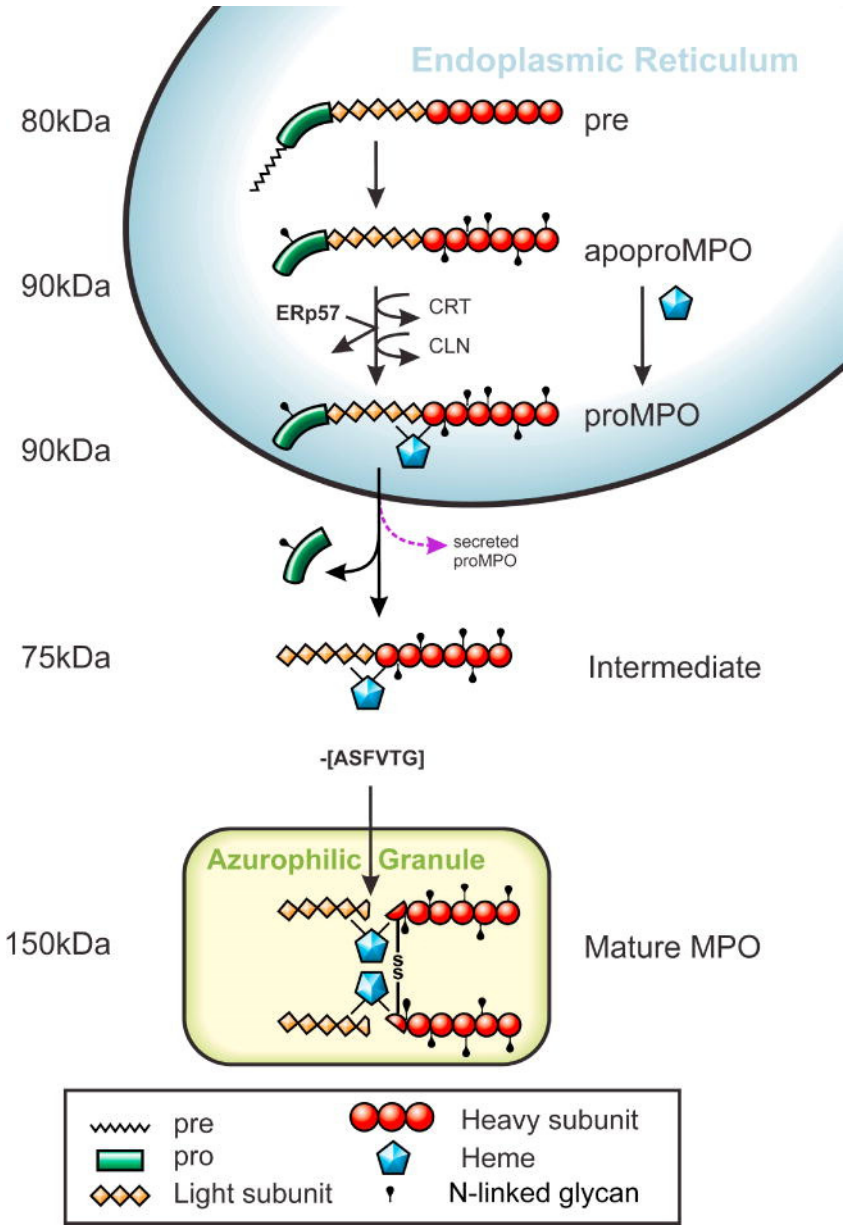

Figure 2. Overview of MPO biosynthesis[9].

MPO and Immune System

Various studies have proven that MPO takes over a major part of the microbicidal activity of immune cells, including neutrophils and monocytes, which takes place through the production of HOCl. During the inflammatory process, the metabolism of nitric oxide in neutrophils occurs at a high rate, which leads to the production of a high amount of Nitrogen Dioxide (NO2). These along with halide ions, create a suitable substrate for the peroxidase activity of MPO, which *in vitro* studies also indicate that this complex can be a powerful anti-microbial system. If the amount of halides is significantly reduced, the germicidal effect of neutrophils decreases, but in neutrophils without MPO, the reduction of halides does not affect the power of neutrophils. Of course, it is worth mentioning that the presence of Hydrogen peroxide (H2O2) is necessary for the proper functioning of this system so that in the case of catalase enzyme and the reduction of this substance, the phagocytic activity of neutrophils is reduced. Of course, this fact is evident that excessive production of oxidants is associated with a series of diseases characterized by inflammation. For example, it has been observed that HOCl leads to an increase in the production of tumor necrosis factor alpha (TNF-α) by altering the function of immune cells [14–16].

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Modulation of inflammatory responses is not limited here, and even other activities of lymphocytes, including reduction of mitogenic proliferation and cytotoxic effects, are affected by MPO-derived oxidants. In addition, MPO is also related to the adhesion and communication between other cells and leukocytes, but this can be changed by using monoclonal antibodies. Moreover, *in vitro* studies have shown that the MPO binding to CD11b/CD18 integrin causes delayed apoptosis of neutrophils and prolonged inflammatory responses by induction of extracellular signal-activated kinase and Akt signaling. Interestingly, in experimental models of diseases related to acute inflammation, such as ischemic reperfusion, the reduction of MPO results in a drastic reduction in clinical and pathological symptoms, including neutrophil accumulation. Collectively, overexpression of MPO whether through the overproduction of oxidants or by functional modulation of immune cells can contribute to the development of cancers, tissue damage, and prolongation of inflammatory responses [7,17,18]?

MPO in Diseases

MPO enzyme plays an important role in many physiological and pathological processes (Table 1), some of which are discussed below: [14,19–28]

Table 1. Summary of the pathological or protective role of MPO in various disorders.

Diseases	Results	Pathological/Protective Role
Colon Cancer	High levels of MPO was observed in CRC tumors that can be considered as worse survival factor in patients [29].	Pathological Role
Breast Cancer	Penetration of MPO-positive cells is a new factor for improving survival of patients with breast cancer [20]	Protective Role
Lung Cancer	Inhibition of MPO leads to reducing size and number of lung tumors and can be used as a protection agent of lung cancer [30]	Pathological Role
Pancreatic Cancer	Increasing levels of NETs (such as MPO) are significantly related to tumor progression and malignancy of Pancreatic ductal adenocarcinoma [31]	Pathological role
Arthrosclerosis	MPO contributes to arteriosclerosis by disrupting the function of endothelial cells, oxidation of LDL, and a high level of MPO is observed in all lesions of this disease [32].	Pathological Role
Myocardial Infarction	Reduced level of MPO and neutrophils is significantly contributed to decreased amount of myocardial infarction injury [33]	Pathological Role
Heart Failure	Irreversible inhibition of MPO leads to reduced rate of heart failure injuries and also improving quality of life in patients with heart failure [34]	Pathological Role
Alzheimer Disease	The increase in the adhesion of neutrophils and the amount of MPO caused by neutrophils causes	Pathological Role

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	vascular oxidative stress and can be one of the therapeutic goals of Alzheimer's disease [35].	
Multiple Sclerosis	Patients with multiple sclerosis have shown low serum levels of MPO, and low levels of MPO play an important role in the pathogenesis of this disease [36].	Protective Role
Parkinson Disease	High levels of MPO is observed in some brain areas related to this disease (such as putamen, caudate nucleus, and substantianigra) [37]	Pathological Role

MPO and Cancer

Among the various diversity in the microenvironment surrounding the tumor, one of the most important ones is neutrophils, which seems to play a significant role in tumor survival or destruction. MPO has received much attention as one of the enzymes secreted by neutrophils. Although the exact role of MPO in tumor pathophysiology has not yet been determined, most studies have proven its enhancing effect on tumor occurrence and growth. This role can be based on the production of oxidants derived from MPO, which can lead to oxidation and mutation of the DNA molecule[38]. There is cumulative evidence indicate that MPO-derived oxygen radical can impair the proper function of natural killer cells which play a significant role in the innate host defense and immune surveillance by mediating antibody-dependent and -independent cytotoxicity towards tumors and viral-infected cells[39]. Accordingly, over-expression of MPO is expected to elevate risks of tumorigenesis through suppression of natural killer (NK) cells involved in immune surveillance. Also, the observation of neutrophilia is one of the signs of difficult treatment in patients with lung cancer. The MPO-derived active species cause the formation of free radicals centered on DNA and ultimately DNA oxidation. In addition, MPO plays an effective role in the occurrence and growth of lung tumors by converting environmental pollutants and procarcinogenic substances into carcinogens. Some studies also show the role of MPO in inhibiting damaged DNA repair mechanisms [14,40].Over activity of MPO during chronic inflammations has been also demonstrated to be involved in tumorigenesis through induction of a hyper-mutagenic environment following interaction of MPO-derived oxidants with DNA resulting in DNA modification[41].

A study on the role of MPO in the incidence and treatment of colorectal cancer has shown that the amount of MPO in these patients has increased significantly and has a direct relationship with the degree of malignancy and cancer progression. Also, by confirming the correlation of MPO level with the number of peripheral neutrophils, this study has proven that the high level of neutrophils directly reduces the survival rate of patients. The high level of MPO can be considered a poor prognosis factor in patients with colorectal cancer [29,42]. Investigating the association between neutrophil infiltration and incidence of colitis-associated colorectal cancer revealed that higher levels of MPO and neutrophil infiltration boost the switching of ulcerative colitis to colorectal cancer [43]. Examining the effects of MPO in mice breast cancer has also shown that the stimulation of MPO and eosinophil peroxidase increases the size and number of breast tumors, and it also has a direct effect on increasing the transcription of metastatic genes and leads to increment in occurrence of metastasis and level of angiogenesis[44]. Also, the presence of NETs (especially MPO) in the microenvironment of high-grade serous ovarian cancer (HGSOC) contributed to the progression of disease in a way that NETosis is supposed to play a vital role in the occurrence of metastasis in the early stages of HGSOC. Hence, MPO could be used as a precise biomarker for ovarian cancer diagnosis [45,46]. During a study on the lung cancer of mice, it was observed that if a MPO inhibitor, N-acetyl lysyltyrosylcysteine amide, (KYC) is used, a reduction in the incidence of lung tumors occurs. Also, this study proved that in MPO-deficient mice, lung carcinoma tumor growth was significantly lower than in other groups[30]. An evaluation of the level of MPO, paraoxonase, and High-density

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lipoprotein (HDL) levels in acute myeloid leukemia confirmed the vital role of MPO, inflammation, and oxidative stress in the pathogenesis of this disease and these parameters can be considered as a prediction of response to chemotherapy[47].

Among the mechanisms of anti-tumor activity of neutrophils, we can mention the anti-oncogenic role of HOCL produced by MPO, which induces cancer cell death. This function is due to the production of types of superoxide anion from tumor cells, which in reaction with HOCL leads to the production of hydroxyl radicals that enhance apoptosis. But tumor cells prevent this process by producing a series of membrane catalases. Here, it is possible to prevent the inhibition of the apoptosis process and even strengthen it by using catalase inhibitors. Among the other mechanisms of MPO in increasing the proliferation rate of cancer cells and the occurrence of malignancy, we can mention the oxidation of cell matrix components due to the oxidants derived from MPO, which causes a decrease in adhesion, and ultimately changes in the proliferation rate of endothelial cells and cell migration[14,29,41,48,49].

MPO and Cardiovascular Diseases

Vascular endothelium is one of the most important targets of MPO and MPO-derived oxidants. For example, in atherosclerosis, an increase in MPO levels has been identified as one of the most important causes of tissue destruction, and with the use of antibodies against HOCl-LDL, the severity and extent of tissue damage are reduced[23,50].Some studies have shown the relationship between increased levels of MPO and disruption of vascular endothelial function, for example, oxidants derived from MPO can cause damage to vascular endothelium by reducing the bioavailability of nitric oxide (NO), which is the result of changes in the expression of the relevant gene or the change in the availability of the substrate for the synthesis of endothelial NO[5]. Furthermore, the vascular injuries caused by MPO can also arise from the facilitation of atherosclerotic plaque development in foamy macrophages, the instability of atherosclerotic plaques due to the activation of matrix metalloproteinase (MMP), and the interactions of P-selectin that induce local occlusive thrombosis [51]. Effect on intracellular signaling cascades is one of the other ways of MPO function for endothelial damage and inflammation exacerbation. MPO, by activating the Rho kinase signaling pathway, can disrupt the dilation of blood vessels and increase the pressure of the right ventricle, which causes an increase in arterial blood pressure, or MPO, by activating calpains, increases the expression of the adhesion molecules of blood vessels and as a result increases the adhesion of leukocytes to the endothelium. The increase in the level of HOCL in the sub-endothelium due to the increase in the amount of MPO and the stimulation of apoptosis of endothelial cells causes the instability of the formed plaques and the occurrence of thrombogenesis [52].

In addition, modification of low-density lipoproteins (LDL) and HDL by MPO and its derivative oxidants increases the proatherogenic function of LDL and decreases the cardioprotective effect of HDL, both of which contribute to the occurrence of atherosclerosis. LDL modified by HOCl causes the accumulation of cholesterol and sterols due to recognition by macrophages. In addition, damage to the vascular endothelium may occur due to increased adhesion of macrophages to this type of LDL and decreased production of NO. The binding of MPO to Apo lipoprotein A1 disrupts HDL function in two ways. This connection disrupts the acceptance of this Apo lipoprotein, and on the other hand, it promotes the pro-inflammatory profile of the endothelial vessels. Also, the presence of HDL modified by MPO reduces the activity of vascular smooth muscle cells (VSMC), which leads to the instability of the plaques formed in the vessels[53]. Furthermore, it has been observed that the presence of MPO-derived oxidants disrupts the anti-apoptotic activity of HDL and reduces the protective activity of HDL in atherosclerotic plaques [3,23,54].

Today, to diagnose acute coronary syndrome, in addition to checking cardiac troponin, the level of MPO is also measured in patients presenting with angina symptoms, because it has been observed that in some cases, even with the presence of negative cardiac troponin, a high level of MPO indicates the occurrence of this disease[14,55].In the pathogenesis of atrial fibrillation (AF), elevated levels of MPO expression occurred and both MPO and neutrophil levels are much higher in patients with persistent AF and this makes measurement a good criterion for predicting AF[56]. Also, the increased

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level of MPO played an important role in a switch of AF phenotype and relapse after catheter ablation[57]. Generally, high levels of MPO contributed to the increased rate of cardiomyopathy, ischemic stroke, heart failure (HF), Myocardial infarction (MI), Ventricular Tachycardia (VT) and AF [58–64]. So it can be considered a therapeutic target in the treatment of cardiovascular disorders such as coronary artery diseases and future studies should specify whether the immunoeffective role of MPO overweigh the atherogenic effect of this biomarker [65].

Previous studies about the effects of different drugs on cardiovascular diseases demonstrated that a decrease in the level of MPO is associated with the protective effects. We have shown in our previous studies, that metformin administration in myocardial infarction, in addition to reducing fibrosis and cardiac remodeling, causes a significant decrease in MPO and TNF-α levels in rats[66]. Also, regarding the protective effects of memantine in heart failure in rats, in addition to reducing cardiac remodeling and lipid peroxidation, another mechanism of action of memantine was the reduction of MPO[67].Other experimental studies, investigating the effects of different plant extracts on myocardial infarction also showed the protective mechanisms of *Arum orientale* and *Marrubiumvulgare*by reducing the level of inflammation, lipid peroxidation, infiltration of neutrophils and the level of MPO[68,69].Administration of memantine as a protective agent in myocardial infarction in rats, also, showed that this protective effect contributed to the reduction in the level of MPO, malondialdehyde, and TNF-α [70].

MPO and Nervous System

Various studies emphasize the role of MPO in the pathogenesis of neurodegenerative diseases, which is mostly through the oxidative damage of MPO-derived oxidants. This oxidative damage includes damage to all cellular components such as proteins, carbohydrates, lipids, and nucleic acids, which ultimately occurs due to excessive production of free radicals, cell disorder, and apoptosis[71,72]. For example, an increase in the level of MPO and the occurrence of lipid peroxidation in the brain tissue of patients with Alzheimer's, MS, and Parkinson's diseases have been observed, and in Alzheimer's disease, the presence of active MPO is mostly seen in the location of beta amyloids and microglia[73,74]. Furthermore, in the lesional tissue of patients with MS, which is considered a degenerative inflammatory disease, protein and mRNA expression of MPO has been observed in microglia and macrophages[75]. Although there are conflicting data about the role of MPO in MS, the supportive role of MPO is in the occurrence of disturbance in the normal activity of the immune system[76,77].It has been observed that the severity of neuronal damage is associated with the expression of the MPO gene and higher levels of inflammation and oxidative stress in MS[78].Among other diseases in which the role of MPO in its pathogenesis has been established is Parkinson's disease, in which increased expression of MPO is observed in the glial cells of dopaminergic neurons, which indicates the role of MPO and its derived oxidants in Parkinson's neurotoxic process[37,79].Elevated levels of NOX4 (one of the reactive oxidative species) in cooperation with MPO are the vital components in progression of neuroinflammation during Parkinson disease[80].Also, a recent study about depression showed that the expression of MPO gene in both mRNA and protein levels elevated significantly in people with depressive disorders revealing the important role of MPO in regulation of cognitive processes[81].

The previous studies of our research team with different drugs that have shown neuroprotective effects of cerebral ischemia/reperfusion all indicate the reduction of MPO activity as one of the mechanisms involved in these protective effects. For example, metformin by decreasing the levels of MPO, malondialdehyde, and leukocyte infiltration reduces cerebral ischemia /reperfusion-induced injuries[82].A similar study demonstrated that the neuroprotective effect of canagliflozin in cerebral cortex injury is associated with lower levels of cortical MPO, malondialdehyde, TNF-alpha, and Interleukin-6[83]. A recent study on the effects of diltiazem and metoprolol in cerebral ischemia-reperfusion injuries also showed that the use of these two drugs alone or in combination, in addition to reducing the infarct size, also caused a significant reduction in MPO levels[84].The administration of bisoprolol and vitamin E alone and in combination, and also in another study hydroxychloroquine, demonstrated protective effects via a significant decrease in the amount of MPO and Malodialdehyde

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(MDA), which even protected the memory and learning ability of mice[85,86]. Furthermore, a clinical study about rupturing cerebral aneurysms, revealed that the MPO level was higher in tissues with rupture in comparison to non-ruptured ones, which demonstrates the association of high levels of oxidative stress and inflammation with rupturing cerebral aneurysms [87]. Even, it proved that lower levels of MPO in stroke are along with a decreased level of inflammation and oxidative brain damage and elevated level of cellular protection[88,89].It has also reported that inhibition the enzyme form of MPO increased the neurogenesis and cell proliferation after ischemic stroke[90]So, these results lead us to consider MPO as a treatment and prevention target in stroke[91]. Even more, a recent study showed that serum lipoprotein-associated phospholipase A2 (Lp-PLA2) combined with MPO could be a valuable predictor of the occurrence of cerebral infarction induced by atherosclerosis and this confirmed the diagnostic value of MPO in stroke-related diseases [92].

MPO Inhibition

Considering the important role of MPO in causing and aggravating inflammation, various studies have been conducted to investigate methods to modulate MPO activity to treat various diseases. Among these methods, the use of MPO inhibitors, limiting substrate availability, and increasing H2O2 removal can be mentioned [93].

Due to the high availability of H2O2 inside the body, if its amount is decreased by enzymes such as peroxiredoxins and catalases, the production of free radicals derived from MPO is reduced. It is also possible to decrease H2O2 levels by inhibiting NADPH oxidase, which plays a role in converting O2 to superoxide anion. In addition, replacing other substrates such as NO2 and Thiocyanate (SCN) can inhibit the production of HOCl by MPO, which results in weaker oxidants with lower performance. Even in mice prone to atherosclerosis, in which high expression of MPO is observed, replacing SCN leads to a significant reduction of plaques and MPO inhibition is one of the new methods in this regard[22,93].

Various non-specific inhibitors such as various drugs, relaxants, antioxidants, and natural products such as flavonoids can act as substrates of peroxidases and remove MPO from the halogenation cycle. For example, it has been proven that the use of quercetin (a flavonoid) can reduce vascular endothelial damage caused by MPO-mediated HOCL[94]. Therewith, the use of cyclic nitroxides as enzyme substrates in a myocardial inflammation model can significantly reduce HOCl production, or the use of peptide N-acetyl lysyltyrosyl cysteine amide (KYC) as a reversible inhibitor of MPO leads to produce lower amounts of MPO-derived HOCl [95–97].

Furthermore, some non-selective inhibitors prevent its activity by binding to MPO, among which ceruloplasmin containing copper in plasma or heparin, which is considered an anticoagulant, by electrostatically adhering to MPO, can be mentioned. It reduces its activity and causes less plaque transfer in patients with stable coronary artery disease[98].Some other compounds act competitively as HOCl targets, including taurine. If the concentration of taurine in neutrophils increases, the infiltration of macrophages and the fragmentation of elastin decrease, which ultimately leads to a reduction in the expression of MPO in patients with abdominal aortic aneurysm. Similarly, some compounds containing selenium react quickly with MPO-derived oxidants and produce selenoxides that are easily recycled by cellular regenerators and antioxidant enzymes[99,100].

Suicide substrates are among the most effective and specific MPO inhibitors. For example, hydrazines and hydrazides act by irreversible degradation of MPO, which, of course, are highly toxic and are rarely used *in vivo*. For example, 4-aminobenzoic acid hydrazide inhibits MPO activity by producing iron-MPO complexes. It disrupts and reduces inflammation and vascular stress and reduces infarct size in stroke models, but on the other hand, it also destroysheme groups. Thioxanthenes are another group of compounds that prevent the production of HOCl by using covalent and irreversible binding to MPO and changing it. These compounds have very high reaction power and act quickly. Recently, AZM 198, which is one of the derivatives of these compounds, has been used for atherosclerosis, which has completely inhibited the MPO function and reduced plaque instability in atherosclerosis. Also, this compound can be effective in increasing pulmonary artery blood pressure due to its ability to reduce the activation of Rhokinase related to MPO[101–103].At

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biomarker level, also, administration of AZD4831 (MPO inhibitor) caused a reduction in the progression of heart failure with preserved ejection fraction (HFpEF) [104]. Even in tumor therapy, it has been observed that inhibition of MPO is an effective way to reduce the resistance of patients to immune-check point therapies and it can be so beneficial in cancer treatment [105]. A better understanding of MPO inhibitory mechanisms can lead us to design new drugs to reduce inflammation and thus moderate the progress of inflammation-related diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease[106].

Concluding remarks

MPO is a peroxidase enzyme containing a heme group, which is found in neutrophils and small amounts in monocytes and takes over a major part in their anti-microbicidal activity. High levels of MPO have been identified as one of the most important causes of tissue destruction, and its inhibition reduces the severity and extent of tissue damage. Over activity of MPO contributes to the development and progression of cancer. Also, high levels of MPO contributed to the increased rate of cardiomyopathy, ischemic stroke, HF, MI, and AF. So it can be considered a therapeutic target in the treatment of cardiovascular disorders.

MPO also participates in the pathogenesis of neurodegenerative diseases. For example, an increase in the level of MPO in the brain tissue of patients with Alzheimer's, MS, and Parkinson's diseases has been observed, and these results lead us to consider MPO as a treatment and prevention target for neurological disorders. Therefore, it is suggested that the role of MPO as a biomarker and a therapeutic target should be given more attention.

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References

1. Németh T, Sperandio M, Mócsai A. Neutrophils as emerging therapeutic targets. Nature reviews Drug discovery. 2020;19(4):253-75.
2. Aroca-Crevillén A, Adrover JM, Hidalgo A. Circadian features of neutrophil biology. Frontiers in Immunology. 2020;11:576.
3. Hawkins CL, Davies MJ. Role of myeloperoxidase and oxidant formation in the extracellular environment in inflammation-induced tissue damage. Free Radical Biology and Medicine. 2021;172:633-51.
4. Fousert E, Toes R, Desai J. Neutrophil extracellular traps (NETs) take the central stage in driving autoimmune responses. Cells. 2020;9(4):915.
5. Ndrepepa G. Myeloperoxidase–A bridge linking inflammation and oxidative stress with cardiovascular disease. Clinica chimica acta. 2019;493:36-51.
6. Levine AP, Segal AW. The NADPH oxidase and microbial killing by neutrophils, with a particular emphasis on the proposed antimicrobial role of myeloperoxidase within the phagocytic vacuole. Myeloid Cells in Health and Disease: A Synthesis. 2017:599-613.
7. Van der Veen BS, de Winther MP, Heeringa P. Myeloperoxidase: molecular mechanisms of action and their relevance to human health and disease. Antioxidants & redox signaling. 2009;11(11):2899-937.
8. Ramirez DC, Gomez Mejiba SE. Pulmonary Neutrophilic Inflammation and Noncommunicable Diseases: Pathophysiology, Redox Mechanisms, Biomarkers, and Therapeutics. Antioxidants & Redox Signaling. 2020;33(3):211-27.
9. Nauseef WM. Biosynthesis of human myeloperoxidase. Arch Biochem Biophys. 2018;642:1-9.
10. Arnhold J. The Dual Role of Myeloperoxidase in Immune Response. Int J Mol Sci. 2020;21(21).
11. Bradley PP, Priebat DA, Christensen RD, Rothstein G. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. Journal of investigative dermatology. 1982;78(3):206-9.

 doi:10.20944/preprints202409.0157.v1

12. Chen S-M, Wang M-H, Soung H-S, Tseng H-C, Fang C-H, Lin Y-W, et al. Neuroprotective effect of l-theanine in a rat model of chronic constriction injury of sciatic nerve-induced neuropathic pain. Journal of the Formosan Medical Association. 2022;121(4):802-14.
13. Majid R, Al Talebi ZA, Al-Kawaz HS, Alta'ee AH, Alsalman ARS, Hadwan AM, et al. Novel fluorometric protocol for assessing myeloperoxidase activity. Enzyme and Microbial Technology. 2023;171:110320.
14. Valadez-Cosmes P, Raftopoulou S, Mihalic ZN, Marsche G, Kargl J. Myeloperoxidase: Growing importance in cancer pathogenesis and potential drug target. Pharmacology & Therapeutics. 2022;236:108052.
15. Rizo-Téllez SA, Sekheri M, Filep JG. Myeloperoxidase: regulation of neutrophil function and target for therapy. Antioxidants. 2022;11(11):2302.
16. Aratani Y. Myeloperoxidase: Its role for host defense, inflammation, and neutrophil function. Archives of biochemistry and biophysics. 2018;640:47-52.
17. El Kebir D, József L, Pan W, Filep JnG. Myeloperoxidase delays neutrophil apoptosis through CD11b/CD18 integrins and prolongs inflammation. Circulation research. 2008;103(4):352-9.
18. Victor VM, Rovira-Llopis S, Banuls C, Diaz-Morales N, Martinez de Maranon A, Rios-Navarro C, et al. Insulin resistance in PCOS patients enhances oxidative stress and leukocyte adhesion: role of myeloperoxidase. PLoS One. 2016;11(3):e0151960.
19. Wang W-w, Wu L, Lu W, Chen W, Yan W, Qi C, et al. Lipopolysaccharides increase the risk of colorectal cancer recurrence and metastasis due to the induction of neutrophil extracellular traps after curative resection. Journal of Cancer Research and Clinical Oncology. 2021;147(9):2609-19.
20. Zeindler J, Angehrn F, Droeser R, Däster S, Piscuoglio S, Ng CK, et al. Infiltration by myeloperoxidase-positive neutrophils is an independent prognostic factor in breast cancer. Breast cancer research and treatment. 2019;177:581-9.
21. Oshima Y, Sano M, Kajiwara I, Ichimaru Y, Itaya T, Kuramochi T, et al. Midazolam exhibits antitumour and anti-inflammatory effects in a mouse model of pancreatic ductal adenocarcinoma. British journal of anaesthesia. 2022;128(4):679-90.
22. Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. Medical sciences. 2018;6(2):33.
23. Frangie C, Daher J. Role of myeloperoxidase in inflammation and atherosclerosis. Biomedical reports. 2022;16(6):1-11.
24. Ramachandra CJ, Ja KMM, Chua J, Cong S, Shim W, Hausenloy DJ. Myeloperoxidase as a multifaceted target for cardiovascular protection. Antioxidants & redox signaling. 2020;32(15):1135-49.
25. Janus SE, Hajjari J, Chami T, Karnib M, Al-Kindi SG, Rashid I. Myeloperoxidase is independently associated with incident heart failure in patients with coronary artery disease and kidney disease. Current Problems in Cardiology. 2022;47(11):101080.
26. Smyth LC, Murray HC, Hill M, van Leeuwen E, Highet B, Magon NJ, et al. Neutrophil-vascular interactions drive myeloperoxidase accumulation in the brain in Alzheimer's disease. Acta Neuropathologica Communications. 2022;10(1):1-17.
27. Li A, Wu Y, Pulli B, Wojtkiewicz GR, Iwamoto Y, Wang C, et al. Myeloperoxidase molecular MRI reveals synergistic combination therapy in murine experimental autoimmune neuroinflammation. Radiology. 2019;293(1):158-65.
28. Maki RA, Holzer M, Motamedchaboki K, Malle E, Masliah E, Marsche G, et al. Human myeloperoxidase (hMPO) is expressed in neurons in the substantia nigra in Parkinson's disease and in the hMPO-α-synuclein-A53T mouse model, correlating with increased nitration and aggregation of α-synuclein and exacerbation of motor impairment. Free Radical Biology and Medicine. 2019;141:115-40.
29. Weng M, Yue Y, Wu D, Zhou C, Guo M, Sun C, et al. Increased MPO in colorectal cancer is associated with high peripheral neutrophil counts and a poor prognosis: A TCGA with propensity score-matched analysis. Frontiers in Oncology. 2022;12:940706.
30. Rymaszewski AL, Tate E, Yimbesalu JP, Gelman AE, Jarzembowski JA, Zhang H, et al. The role of neutrophil myeloperoxidase in models of lung tumor development. Cancers. 2014;6(2):1111-27.
31. Mitsis M, Drosou P, Tatsis V, Markopoulos GS. Neutrophil extracellular traps and pancreatic cancer development: a vicious cycle. Cancers. 2022;14(14):3339.
32. Tangeten C, Zouaoui Boudjeltia K, Delporte C, Van Antwerpen P, Korpak K. Unexpected role of MPO-oxidized LDLs in atherosclerosis: In between inflammation and its resolution. Antioxidants. 2022;11(5):874.

 doi:10.20944/preprints202409.0157.v1

33. Zhang N, Aiyasiding X, Li W-j, Liao H-h, Tang Q-z. Neutrophil degranulation and myocardial infarction. Cell Communication and Signaling. 2022;20(1):50.
34. Inghardt T, Antonsson T, Ericsson C, Hovdal D, Johannesson P, Johansson C, et al. Discovery of AZD4831, a mechanism-based irreversible inhibitor of myeloperoxidase, as a potential treatment for heart failure with preserved ejection fraction. Journal of Medicinal Chemistry. 2022;65(17):11485-96.
35. Smyth LC, Murray HC, Hill M, van Leeuwen E, Highet B, Magon NJ, et al. Neutrophil-vascular interactions drive myeloperoxidase accumulation in the brain in Alzheimer's disease. Acta neuropathologica communications. 2022;10(1):38.
36. Bilge N, Yevgi R, Kızıldağ N, Kızıltunç A. Low Serum Myeloperoxidase Levels in Multiple Sclerosis Patients. New Trends in Medicine Sciences. 2021;2(1):63-8.
37. Gellhaar S, Sunnemark D, Eriksson H, Olson L, Galter D. Myeloperoxidase-immunoreactive cells are significantly increased in brain areas affected by neurodegeneration in Parkinson's and Alzheimer's disease. Cell and tissue research. 2017;369:445-54.
38. Scandolara TB, Panis C. Neutrophil traps, anti-myeloperoxidase antibodies and cancer: Are they linked? Immunology Letters. 2020;221:33-8.
39. Betten Å, Dahlgren C, Mellqvist U-H, Hermodsson S, Hellstrand K. Oxygen radical-induced natural killer cell dysfunction: role of myeloperoxidase and regulation by serotonin. Journal of Leucocyte Biology. 2004;75(6):1111-5.
40. Aloe C, Wang H, Vlahos R, Irving L, Steinfort D, Bozinovski S. Emerging and multifaceted role of neutrophils in lung cancer. Transl Lung Cancer Res. 2021;10(6):2806-18.
41. Vanhamme L, Boudjeltia KZ, Van Antwerpen P, Delporte C. The other myeloperoxidase: Emerging functions. Archives of biochemistry and biophysics. 2018;649:1-14.
42. Feng C, Li Y, Tai Y, Zhang W, Wang H, Lian S, et al. A neutrophil extracellular traps-related classification predicts prognosis and response to immunotherapy in colon cancer. Sci Rep. 2023;13(1):19297.
43. Zhang C, Zhang J, Zhang Y, Song Z, Bian J, Yi H, et al. Identifying neutrophil-associated subtypes in ulcerative colitis and confirming neutrophils promote colitis-associated colorectal cancer. Front Immunol. 2023;14:1095098.
44. Panagopoulos V, Leach DA, Zinonos I, Ponomarev V, Licari G, Liapis V, et al. Inflammatory peroxidases promote breast cancer progression in mice via regulation of the tumour microenvironment. International journal of oncology. 2017;50(4):1191-200.
45. Tomás-Pérez S, Oto J, Aghababyan C, Herranz R, Cuadros-Lozano A, González-Cantó E, et al. Increased levels of NETosis biomarkers in high-grade serous ovarian cancer patients' biofluids: Potential role in disease diagnosis and management. Front Immunol. 2023;14:1111344.
46. Saed GM, Nawaz A, Alvero AA, Harper AK, Morris RT. Monomeric myeloperoxidase is a specific biomarker for early-stage ovarian cancer. Biomarkers. 2023;28(7):663-71.
47. Sincan S, Sincan G, Aşkın S, Kızıltunç A. Evaluation of Serum Paraoxonase, Myeloperoxidase, and HDL-Cholesterol Levels in Acute Myeloid Leukemia. Inflammation. 2023;46(6):2470-6.
48. Andrés CMC, Pérez de la Lastra JM, Andrés Juan C, Plou FJ, Pérez-Lebeña E. Superoxide Anion Chemistry-Its Role at the Core of the Innate Immunity. Int J Mol Sci. 2023;24(3).
49. Bauer G. HOCl-dependent singlet oxygen and hydroxyl radical generation modulate and induce apoptosis of malignant cells. Anticancer Res. 2013;33(9):3589-602.
50. Nadel J, Jabbour A, Stocker R. Arterial myeloperoxidase in the detection and treatment of vulnerable atherosclerotic plaque: a new dawn for an old light. Cardiovasc Res. 2023;119(1):112-20.
51. Wang Y-C, Lu Y-B, Huang X-L, Lao Y-F, Zhang L, Yang J, et al. Myeloperoxidase: a new target for the treatment of stroke? Neural Regeneration Research. 2022;17(8):1711.
52. Sugiyama S, Kugiyama K, Aikawa M, Nakamura S, Ogawa H, Libby P. Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis. Arterioscler Thromb Vasc Biol. 2004;24(7):1309-14.
53. Prokopowicz Z, Marcinkiewicz J, Katz DR, Chain BM. Neutrophil myeloperoxidase: soldier and statesman. Archivum immunologiae et therapiae experimentalis. 2012;60:43-54.
54. Varadhan S, Ramesh V, Jawahar R, Pai MM, Simon AS. OxLDL/HDL ratio and its correlation to myeloperoxidase activity in ACS patients. International Journal of Health Sciences. (II):10438-46.

 doi:10.20944/preprints202409.0157.v1

55. Jaiswal A, Doctor B, Verma MK, Vamne A. Myeloperoxidase and troponin T are linked with myocardial infarction among young Indians. Bioinformation. 2022;18(1):66.
56. Meulendijks ER, Al-Shama RFM, Kawasaki M, Fabrizi B, Neefs J, Wesselink R, et al. Atrial epicardial adipose tissue abundantly secretes myeloperoxidase and activates atrial fibroblasts in patients with atrial fibrillation. J Transl Med. 2023;21(1):366.
57. Liu J, Lin C, Zhou T, Bao Y, Xie Y, Wei Y, et al. Plasma myeloperoxidase: association with atrial fibrillation progression and recurrence after catheter ablation. Front Cardiovasc Med. 2023;10:1150324.
58. Wang Y, Jia Y, Xu Q, Wang R, Sun L, Guo D, et al. Association between myeloperoxidase and the risks of ischemic stroke, heart failure, and atrial fibrillation: A Mendelian randomization study. Nutr Metab Cardiovasc Dis. 2023;33(1):210-8.
59. Nettersheim FS, Schlüter JD, Kreuzberg W, Mehrkens D, Grimm S, Nemade H, et al. Myeloperoxidase is a critical mediator of anthracycline-induced cardiomyopathy. Basic Res Cardiol. 2023;118(1):36.
60. Newman JD, Anthopolos R, Ruggles KV, Cornwell M, Reynolds HR, Bangalore S, et al. Biomarkers and cardiovascular events in patients with stable coronary disease in the ISCHEMIA Trials. Am Heart J. 2023;266:61-73.
61. Zhang N, Aiyasiding X, Li WJ, Liao HH, Tang QZ. Neutrophil degranulation and myocardial infarction. Cell Commun Signal. 2022;20(1):50.
62. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2005;25(6):1102-11.
63. Mollenhauer M, Friedrichs K, Lange M, Gesenberg J, Remane L, Kerkenpaß C, et al. Myeloperoxidase mediates postischemic arrhythmogenic ventricular remodeling. Circulation research. 2017;121(1):56-70.
64. Smorodinova N, Blaha M, Melenovský V, Rozsivalova K, Přidal J, Ďurišová M, et al. Analysis of immune cell populations in atrial myocardium of patients with atrial fibrillation or sinus rhythm. PLoS One. 2017;12(2):e0172691.
65. Chaikijurajai T, Tang WHW. Myeloperoxidase: a potential therapeutic target for coronary artery disease. Expert Opin Ther Targets. 2020;24(7):695-705.
66. Soraya H, Farajnia S, Khani S, Rameshrad M, Khorrami A, Banani A, et al. Short-term treatment with metformin suppresses toll like receptors (TLRs) activity in isoproterenol-induced myocardial infarction in rat: are AMPK and TLRs connected? International immunopharmacology. 2012;14(4):785-91.
67. Abbaszadeh S, Javidmehr A, Askari B, Janssen PM, Soraya H. Memantine, an NMDA receptor antagonist, attenuates cardiac remodeling, lipid peroxidation and neutrophil recruitment in heart failure: A cardioprotective agent? Biomedicine & Pharmacotherapy. 2018;108:1237-43.
68. Javidmehr A, Abbaszadeh S, Kian M, Hamedeyazdan S, Soraya H. Hydroalcoholic extract of Arum orientale ameliorates myocardial infarction induced by isoproterenol in rats. J Res Pharm. 2021;25(1):80-8.
69. Yousefi K, Soraya H, Fathiazad F, Khorrami A, Hamedeyazdan S, Maleki-Dizaji N, et al. Cardioprotective effect of methanolic extract of Marrubium vulgare L. on isoproterenol-induced acute myocardial infarction in rats. 2013.
70. Jannesar K, Abbaszadeh S, Malekinejad H, Soraya H. Cardioprotective effects of memantine in myocardial ischemia: Ex vivo and in vivo studies. European Journal of Pharmacology. 2020;882:173277.
71. Lefkowitz DL, Lefkowitz SS. Microglia and myeloperoxidase: a deadly partnership in neurodegenerative disease. Free Radical Biology and Medicine. 2008;45(5):726-31.
72. Pravalika K, Sarmah D, Kaur H, Wanve M, Saraf J, Kalia K, et al. Myeloperoxidase and neurological disorder: a crosstalk. ACS chemical neuroscience. 2018;9(3):421-30.
73. Ray R, Katyal A. Myeloperoxidase: bridging the gap in neurodegeneration. Neuroscience & Biobehavioral Reviews. 2016;68:611-20.
74. Wright JR, Deen QFE, Stevenson A, Telford-Cooke LL, Parker C, Martin-Ruiz C, et al. Plasma Myeloperoxidase as a Potential Biomarker of Patient Response to Anti-Dementia Treatment in Alzheimer's Disease. J Alzheimers Dis. 2022;89(4):1483-92.
75. Fischer MT, Sharma R, Lim JL, Haider L, Frischer JM, Drexhage J, et al. NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury. Brain. 2012;135(3):886-99.
76. Strzepa A, Pritchard KA, Dittel BN. Myeloperoxidase: A new player in autoimmunity. Cellular immunology. 2017;317:1-8.

 doi:10.20944/preprints202409.0157.v1

77. Arnhold J. The dual role of myeloperoxidase in immune response. International Journal of Molecular Sciences. 2020;21(21):8057.
78. Zakrzewska-Pniewska B, Styczynska M, Podlecka A, Samocka R, Peplonska B, Barcikowska M, et al. Association of apolipoprotein E and myeloperoxidase genotypes to clinical course of familial and sporadic multiple sclerosis. Mult Scler. 2004;10(3):266-71.
79. Mosley RL, Benner EJ, Kadiu I, Thomas M, Boska MD, Hasan K, et al. Neuroinflammation, oxidative stress, and the pathogenesis of Parkinson's disease. Clinical neuroscience research. 2006;6(5):261-81.
80. Boonpraman N, Yoon S, Kim CY, Moon JS, Yi SS. NOX4 as a critical effector mediating neuroinflammatory cytokines, myeloperoxidase and osteopontin, specifically in astrocytes in the hippocampus in Parkinson's disease. Redox Biol. 2023;62:102698.
81. Talarowska M, Szemraj J, Gałecki P. Myeloperoxidase gene expression and cognitive functions in depression. Adv Med Sci. 2015;60(1):1-5.
82. Karimipour M, Zarghani SS, Milani MM, Soraya H. Pre-treatment with metformin in comparison with post-treatment reduces cerebral ischemia reperfusion induced injuries in rats. Bulletin of Emergency & Trauma. 2018;6(2):115.
83. Hassanein EHM, Saleh FM, Ali FEM, Rashwan EK, Atwa AM, Abd El-Ghafar OAM. Neuroprotective effect of canagliflozin against cisplatin-induced cerebral cortex injury is mediated by regulation of HO-1/PPAR-γ, SIRT1/FOXO-3, JNK/AP-1, TLR4/iNOS, and Ang II/Ang 1-7 signals. Immunopharmacol Immunotoxicol. 2023;45(3):304-16.
84. Sadrhaghighi G, Abbaszadeh S, Babataheri S, Garjani A, Soraya H. Effects of pre-treatment with metoprolol and diltiazem on cerebral ischemia/reperfusion-induced injuries. Brazilian Journal of Pharmaceutical Sciences. 2023;58.
85. Salehi C, Seiiedy M, Soraya H, Fazli F, Ghasemnejad-Berenji M. Pretreatment with bisoprolol and vitamin E alone or in combination provides neuroprotection against cerebral ischemia/reperfusion injury in rats. Naunyn-Schmiedeberg's Archives of Pharmacology. 2021;394:685-95.
86. Babataheri S, Malekinejad H, Mosarrezaii A, Soraya H. Pre-treatment or post-treatment with hydroxychloroquine demonstrates neuroprotective effects in cerebral ischemia/reperfusion. Fundamental & Clinical Pharmacology. 2023;37(3):589-98.
87. Acik V, Kulahcı O, Arslan A, İstemen İ, Olguner SK, Arslan B, et al. The Impact of Myeloperoxidase in the Rupturing of Cerebral Aneurysms. World Neurosurg. 2021;147:e105-e10.
88. Kim HJ, Wei Y, Wojtkiewicz GR, Lee JY, Moskowitz MA, Chen JW. Reducing myeloperoxidase activity decreases inflammation and increases cellular protection in ischemic stroke. J Cereb Blood Flow Metab. 2019;39(9):1864-77.
89. Joaquim LS, Danielski LG, Bonfante S, Biehl E, Mathias K, Denicol T, et al. NLRP3 inflammasome activation increases brain oxidative stress after transient global cerebral ischemia in rats. Int J Neurosci. 2023;133(4):375-88.
90. Kim H, Wei Y, Lee JY, Wu Y, Zheng Y, Moskowitz MA, et al. Myeloperoxidase Inhibition Increases Neurogenesis after Ischemic Stroke. J Pharmacol Exp Ther. 2016;359(2):262-72.
91. Maestrini I, Tagzirt M, Gautier S, Dupont A, Mendyk AM, Susen S, et al. Analysis of the association of MPO and MMP-9 with stroke severity and outcome: Cohort study. Neurology. 2020;95(1):e97-e108.
92. Hua M, Chen WY, Wang LH, Zou XH, Mao LL. The value of serum Lp-PLA2 combined with MPO in the diagnosis of cerebral infarction caused by large artery atherosclerosis. Clin Neurol Neurosurg. 2023;232:107899.
93. Galijasevic S. The development of myeloperoxidase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2019;29(1):1-7.
94. Lu N, Sui Y, Tian R, Peng Y-Y. Inhibitive effects of quercetin on myeloperoxidase-dependent hypochlorous acid formation and vascular endothelial injury. Journal of agricultural and food chemistry. 2018;66(19):4933-40.
95. Witting PK. Hypochlorous acid generated in the heart following acute ischaemic injury promotes myocardial damage: a new target for therapeutic development.
96. Chaikijurajai T, Tang WW. Myeloperoxidase: a potential therapeutic target for coronary artery disease. Expert opinion on therapeutic targets. 2020;24(7):695-705.
97. Lazarevic-Pasti T, Leskovac A, Vasic V. Myeloperoxidase inhibitors as potential drugs. Current drug metabolism. 2015;16(3):168-90.

 doi:10.20944/preprints202409.0157.v1

98. Hu H, Keat K. Myeloperoxidase and associated lung disease: Review of the latest developments. International Journal of Rheumatic Diseases. 2021;24(12):1460-6.
99. Kim DG, Kwon YM, Kang IS, Kim C. Taurine chloramine selectively regulates neutrophil degranulation through the inhibition of myeloperoxidase and upregulation of lactoferrin. Amino acids. 2020;52:1191-9.
100. Chen S, Chen H, Du Q, Shen J. Targeting myeloperoxidase (MPO) mediated oxidative stress and inflammation for reducing brain ischemia injury: Potential application of natural compounds. Frontiers in physiology. 2020;11:433.
101. Cheng D, Talib J, Stanley CP, Rashid I, Michaëlsson E, Lindstedt E-L, et al. Inhibition of MPO (myeloperoxidase) attenuates endothelial dysfunction in mouse models of vascular inflammation and atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2019;39(7):1448-57.
102. Ali M, Pulli B, Courties G, Tricot B, Sebas M, Iwamoto Y, et al. Myeloperoxidase inhibition improves ventricular function and remodeling after experimental myocardial infarction. JACC: Basic to Translational Science. 2016;1(7):633-43.
103. Cosic-Mujkanovic N, Valadez-Cosmes P, Maitz K, Lueger A, Mihalic ZN, Runtsch MC, et al. Myeloperoxidase Alters Lung Cancer Cell Function to Benefit Their Survival. Antioxidants (Basel). 2023;12(8).
104. Michaëlsson E, Lund LH, Hage C, Shah SJ, Voors AA, Saraste A, et al. Myeloperoxidase Inhibition Reverses Biomarker Profiles Associated With Clinical Outcomes in HFpEF. JACC Heart Fail. 2023;11(7):775-87.
105. Liu TW, Gammon ST, Yang P, Ma W, Wang J, Piwnica-Worms D. Inhibition of myeloperoxidase enhances immune checkpoint therapy for melanoma. J Immunother Cancer. 2023;11(2).
106. Huang J, Milton A, Arnold RD, Huang H, Smith F, Panizzi JR, et al. Methods for measuring myeloperoxidase activity toward assessing inhibitor efficacy in living systems. Journal of Leucocyte Biology. 2016;99(4):541-8.