Role of MPO in Human Diseases and Inflammation

Subjects: Biochemistry & Molecular Biology

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Myeloperoxidase (MPO), also called hydrogen peroxide oxidoreductase with a particular (EC 1.11.1.7), is an enzyme found in the primary granules of granulocytic cells (neutrophils, eosinophils, and, to a lesser extent, monocytes). Lymphocytes lack MPO enzyme activity. However, the most common sources are neutrophils, where the enzyme is located at the lysosomal level in the azurophil granules.

halogenative stress myeloperoxidase MPO pathologies

1. Introduction

Myeloperoxidase (MPO) is the major component of white blood cells in humans [1]. These leukocytes recognise microorganisms through various receptors that act by stimulating the migration of the cells to the site of infection, promoting the phagocytosis of the microorganisms and stimulating the production of biocidal substances that destroy the microorganisms. A second microbicidal mechanism used by activated leukocytes occurs during the respiratory burst, which involves reducing molecular oxygen to reactive oxygen intermediates (ROS), such as superoxide radicals $^{\bullet}O_2^-$, using the reduced form of NADPH [2]. The superoxide undergoes a disproportionate reaction to give oxygen (O_2) and hydrogen peroxide (H_2O_2), and the latter is used by the MPO enzyme to convert the normally very unreactive halide ions into hypohalous acids that are relatively strong oxidising agents and toxic to bacteria [3]. When intense leukocyte activation occurs, ROS, nitric oxide, and lysosomal enzymes are released, which can injure normal host tissues [4].

MPO is a marker and mediator of inflammation and oxidative stress. An elevated myeloperoxidase level is associated with increased risk, prevalence, and severity, and predicts a poor prognosis in patients with cardiovascular disease. The most common CVD-related actions of MPO are: (i) generation of dysfunctional atherogenic lipoproteins; (ii) reduced NO availability; (iii) endothelial dysfunction; (iv) impaired vasoreactivity; and (v) the instability of the atherosclerotic plaque. This links the MPO levels to the pathophysiology of CVD. Thus, MPO can be considered a mediator or a tool through which inflammation promotes CVD at the molecular and cellular level. MPO can damage host tissue by generating reactive halogenating and nitrating agents [5].

MPO has a detrimental effect during chronic inflammation, and inflammation is reduced in conditions of MPO deficiency. Indeed, this has been observed in many acute and chronic inflammatory diseases. In cases of

inflammatory response to non-infectious stimuli (in the absence of pathogens), several recent studies have shown an increase in the inflammatory process associated with the level of MPO.

Neutrophils and macrophages contribute to myocardial and other tissue injury resulting from post-ischemic reperfusion and inflammation [6]. These actions are mainly due to the production by these cells of HOCl/ClO^-, superoxide $^{\bullet}O_2^-$, and derivatives of $^{\bullet}NO$ [7][8][9][10].

MPO also has other catalytic activities [11]: (a) it reacts with the superoxide $^{\bullet}O_2^-$ generating the oxo-myeloperoxidase which, in the presence of H_2O_2, forms "Compound II"; (b) it complexes $^{\bullet}NO$ and catalyses the production of the $^{\bullet}NO_2$ radical [9][10][11], using the nitrite ion as a substrate; (c) it peroxidises different oxidisable organic molecules, forming the corresponding free radicals [12][13][14]; and (d) it hydroxylates aromatic molecules [15][16].

Lipoamide dehydrogenase (LADH) is a mitochondrial enzyme that is very important for energy generation in cardiac muscle. It is inhibited by oxygen free radicals, making it an optimal target for the active species generated by MPO [15][16][17][18]. These species inactivate LADH and thus may contribute to tissue damage by other oxy-radicals (Fenton reaction) as a consequence of post-ischemic reperfusion or inflammation. Compounds with thiol groups, some of which are used therapeutically, counteract the pro-oxidant action of MPO-dependent systems, as shown in **Figure 1**.

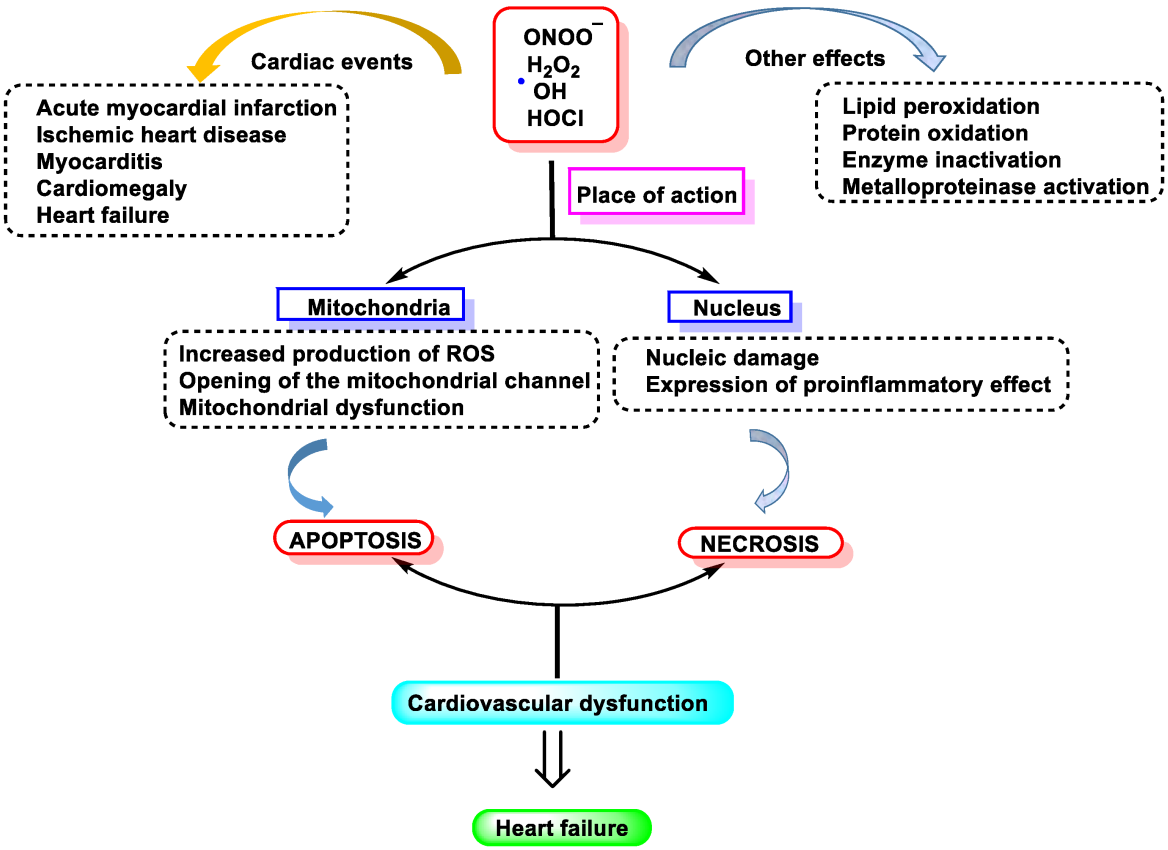

Figure 1. Free radical-induced damage to the cardiovascular system.

2. MPO in Human Diseases

MPO is linked to many aspects of human cardiovascular disease and it is believed that this enzyme acts on both the initiation and propagation of cardiac pathologies [19]. The latter findings agree with results of many other studies that support the concept that MPO plays an important role in the pathogenesis of atherosclerosis and cardiovascular disease. Evidence supports the fact that MPO plays a very important role in the pathogenesis of atherosclerosis because it contributes to vascular dysfunction during acute inflammation by modulating the endothelial NO bioavailability [20]. A recent animal model study of ischaemia-related myocardial damage revealed increases in MPO in arrhythmogenic left ventricular remodelling, as manifested by connexin 43 rupture due to MMP-7 activation and increased post-ischaemic ventricular fibrosis [21]. Thus, MPO contributes to vascular dysfunction by virtue of its capacity to generate potent ROS and to promote the activity of matrix metalloproteinase MMPs [22]

The accumulation of LDL-derived cholesterol in the arterial wall triggers atherosclerosis, the main cause of cardiovascular disease. HDL, on the other hand, delays atherosclerosis by promoting cholesterol efflux. It has been proposed that HDL loses its cardioprotective effects in patients suffering from atherosclerosis [23]. One potential pathway involves oxidative damage by MPO; Baohai Shao et al., 2010, demonstrated that HDL from patients with cardiovascular disease contains high levels of 3-chlorotyrosine and 3-nitrotyrosine, two characteristic products of MPO [24].

MPO and $HOCl^-$ modified proteins have been detected in diseased renal tissue. Mollenhauer et al., 2017, observed a significant reduction in renal function loss after the reperfusion of chemically damaged kidneys in MPO-KO mice compared to WT mice, demonstrating a contribution of MPO in the induction of organ damage after renal ischaemia-reperfusion by influencing critical factors such as neutrophil extravasation [21].

Chronic inflammation plays a key role in tumour promotion in lung cancer. Amy L. Rymaszewski et al., 2014, in mouse studies demonstrated that neutrophils are critical mediators of tumour promotion in methylcholanthrene (MCA)-initiated and butylated hydroxytoluene (BHT)-promoted lung carcinogenesis and subsequently, they investigated the role of neutrophil MPO activity in the inflammation-promoted model, observing increased protein levels and MPO activity in the lungs of mice-administered BHT. An MPO inhibitor reduced tumour burden.

Rotem Volkman et al., 2019, reviewed the body of evidence linking neutrophil-derived MPO in the pathogenesis of Alzheimer's disease (AD), verifying this role in an animal model. They reproduced haematological chimerism in the 5XFAD mouse model of AD with MPO-deficient mice, resulting in 5XFAD with haematological MPO deficiency (5XFAD-MPO KO). Behavioural examinations of 5XFAD-MPO KO mice showed a significantly superior performance in spatial learning and memory, associative learning and anxiety/risk assessment behaviour compared to 5XFAD mice transplanted with WT cells (5XFAD-WT). Immunohistochemical and hippocampal mRNA expression analyses showed significantly reduced levels of inflammatory mediators in 5XFAD-MPO KO mice, with no apparent difference in the number of amyloid-β plaques. In addition, immunoblotting and mRNA analyses showed significantly reduced levels of APOE in 5XFAD-MPO KO mice.

Taken together, their analyses indicate a substantial involvement of neutrophil-derived MPO in the pathogenesis of the 5XFAD model of AD and suggest that MPO is a potential therapeutic target in AD.

In recent years, a significant amount of evidence has implicated a role of MPO in the pathogenesis of atherosclerosis. MPO is an enzymatic source of eicosanoids and bioactive lipids and generates atherogenic forms of low- and high-density lipoproteins. These factors demonstrate that increased systemic levels of MPO and its oxidation products predict increased cardiovascular risk. Consequently, interest has focused on the potential of MPO for the development of new mechanisms to analyse its presence as risk markers, as well as therapies to prevent cardiovascular events. Rachel J. Roth Flach et al., 2019, examined the role of MPO inhibitors in the treatment of heart failure and acute coronary syndrome in humans. The results obtained in their study suggest that MPO inhibition does not alter the atherosclerotic plaque area or leukocyte uptake, but rather alters the inflammatory tone of atherosclerotic lesions; therefore, MPO inhibition has utility in promoting atherosclerotic lesion stabilisation and preventing atherosclerotic plaque rupture [25].

3. MPO and Organ Inflammation

MPO can damage the host tissue by generating reactive halogenating and nitrating agents. Lower levels of 3-chlorotyrosine, 3-bromotyrosine, 3-nitrotyrosine, and protein carbamylation are observed at sites of inflammation in MPO-KO mice compared to WT mice. Therefore, since MPO has a detrimental effect during chronic inflammation, it is to be expected that inflammation is reduced under conditions of MPO deficiency. Indeed, this has been observed in many acute and chronic inflammatory diseases [26].

Recent observations extend this perspective and deeply implicate MPO in the regulation of cellular homeostasis, playing a central role in the initiation and propagation of acute and chronic vascular inflammatory disease. Thus, low levels of HOCl interfere with intracellular signalling, as MPO-dependent lipoprotein oxidation modulates its affinity for macrophages and the vascular wall. Simultaneously, MPO-mediated endothelial NO depletion impairs vasodilation and nitrotyrosine (NO_2Tyr) formation in the vascular wall may affect the structure and function of matrix proteins [27].

The development of imaging techniques to accurately identify MPO localisation and molecular targets of HOCl in vivo is an important advance. Until recently, the involvement of MPO in inflammatory disease has been inferred by its presence, together with the detection of HOCl biomarkers, in biological fluids or diseased tissues. These results provide valuable information regarding the cell types responsible for MPO release in vivo, along with new insight into potential therapeutic opportunities [28].

4. Summary Table of the Relationship between MPO and Different Diseases

As follows, **Table 1** summarises the relationship between MPO and disease (including recent research findings), citing diseases and references.

Table 1. Occurrence of MPO in various diseases.

Disease Classification	Disease and References
Autoimmune Disease	Inflammatory bowel disease/colitis [29][30][31] Rheumatoid arthritis [32][33] Systemic lupus erythematosus [34][35][36]
Neuronal Pathology	Alzheimer's disease [37][38][39] Multiple sclerosis [40][41][42] Neurodegenerative disease [43][44][45] Parkinson's disease [46][47] Stroke [48][49][50]
Cardiovascular Pathology	Atrial fibrillation [51][52] Cardiovascular disease/atherosclerosis [53][54][55] Hypertension [56][57][58] Myocardial infarction [59][60][61] Vascular dysfunction [62][63][64] Asthma [65][66][67]
Pulmonary Pathology	Chronic obstructive pulmonary disease [68][69][70] Cystic fibrosis [71][72][73]
Miscellaneous	Ageing [74][75][76] Cancer [77][78][79] Chronic kidney disease [80][81][82] Inflammation [5][28][83] Lipoprotein modification [30][61][62] Metabolic syndrome/obesity [84][85][86] Type 2 diabetes [86][87][88]

Figure 2, below, summarises what has been explained throughout: chlorinated species have mainly been related to pathologies where the cause is linked to molecular alterations and their effect on inflammatory processes, tissue damage, damage to genetic material, apoptosis, etc.

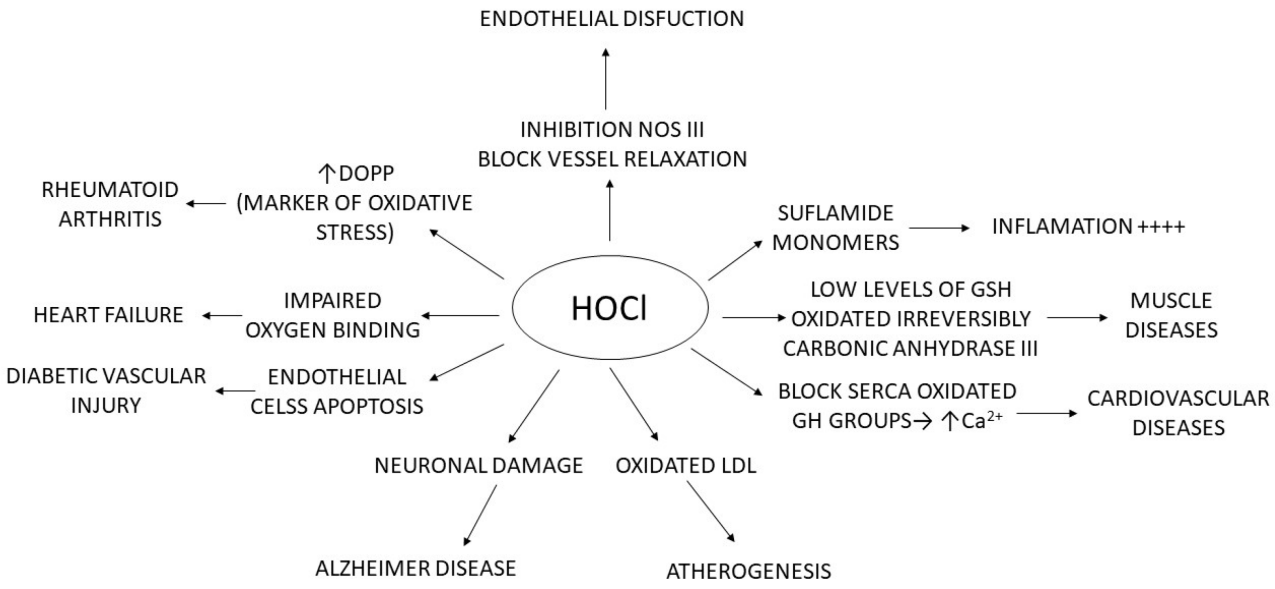

Figure 2. Relationship of HOCl with different pathologies.

5. Myeloperoxidase as a Disease Biomarker

The antibacterial activity of MPO, through the production of HOCl and its controlled release at the site of infection, is of vital importance for its activity to be effective. Its uncontrolled expression overstates inflammation and can lead to tissue damage, even if inflammation does not occur. Several tissue lesions and the pathogenesis of diseases such as rheumatoid arthritis, cardiovascular and liver diseases, diabetes and cancer are linked to MPO-derived HOCl. Therefore, increased MPO activity is a good diagnostic tool for biomarkers of inflammation and oxidative stress [1].

Coordination between several biochemical pathways, including neutrophil activation, $^{\bullet}O_2^-$ production by NADPH oxidase, and MPO release by exocytosis, leads to clearance of bacterial infection [89], as invading bacteria induce increased H_2O_2 production by the enzyme superoxide dismutase SOD, whereby MPO produces HOCl. Both products, H_2O_2 and HOCl, are particularly toxic to invading bacteria. This biochemical phenomenon is called the respiratory burst [90]. When bacterial infection occurs, one of the important mediators of this cascade is formylated peptide, which also acts as a chemoattractant, activating neutrophils via the formylated peptide receptor fPR, a G protein-coupled receptor [91]. The release of H_2O_2 oxidises various substrates, such as halides (Cl^-, Br^-), and pseudohalides (thiocyanate SCN^-) [3][92]. These oxidant species, under normal physiological circumstances, are toxic to several micro-organisms and play an important role in the immune system. Their excessive or deregulated production of oxidants can cause damage to host cells and lead to various diseases [93][94]. The polycationic character of MPO allows it to bind to negatively charged surfaces of pathogens and causes the destruction of their cell membrane, inducing lysis of the bacteria. This enzyme can also bind to other cell surfaces, such as epithelial cells, macrophages, fibroblasts, endothelial cells, platelets, neutrophils, low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL) [95][96].

6. Measurement of MPO Activity

Currently, there is considerable interest in developing “biomarkers” of MPO activity that can be applied to humans. These involve measuring the end products of oxidative damage in different classes of biomolecules or directly determining the production of HOCl. Different types of equipment are currently available on the market. The most common method of measuring MPO is through enzyme-linked immunosorbent assay ELISA kits. Among the different devices, the following are worth mentioning:

Arigo Biolaboratories Corporation (Hsinchu City, Taiwan), developed a MPO/Myeloperoxidase Activity Assay Kit (Colorimetric) that can be used to measure myeloperoxidase activity in whole neutrophils, neutrophil lysates, tissue homogenates, and plasma (EDTA). This colorimetric device bases its principle of operation on the fact that HOCl rapidly reacts with taurine to produce a stable taurine chloramine product. This step neutralises HOCl, which would otherwise accumulate and inactivate MPO. A stop solution containing catalase is added to stop the catalysis of MPO, removing the hydrogen peroxide. Finally, taurine chloramine reacts with the yellow chromogenic probe TNB, with a decrease in colour indicating increased MPO activity. The concentration of MPO in the samples is then determined by comparing the absorbance of the samples at 405–412 nm with the standard curve.

Abcam, at the Cambridge Biomedical Campus, Cambridge, UK, markets a colorimetric kit with similar characteristics to that described above, notably that it can be used to detect MPO as low as 0.05 mU per well.

Cayman Chemical Company, in Ann Arbor, MI, USA, markets a complete assay for the isolation of neutrophils and the measurement of MPO activity that analyses the release of MPO by activated phagocytes and uses TMB as a chromogenic substrate for MPO, including a specific inhibitor of MPO function to verify specificity. This also includes the reagents necessary to isolate neutrophils from human whole blood.

Celltechgen Laboratory, in Houston, TX, USA, is a state-of-the-art medical testing laboratory service that provides a complete range of tests for the diagnosis, screening, or evaluation of diseases and health conditions and markets an MPO Peroxidation Activity Assay Kit, suitable for use as a high-throughput MPO activity assay. The assay kit oxidises a substrate to generate fluorescence (Ex/Em = 571/585 nm), directly proportional to total peroxidase activity in the sample. The assay is high-throughput adaptable and can detect less than 2 µU of MPO activity. This kit can be used to detect MPO activity as low as 0.5 µU per well.

7. Inhibitors of MPO

The microbicidal activity of the MPO enzyme is due to its ability to oxidise halide or pseudohalide ions (X = Cl^-, Br^-, I^- and SCN^-) producing the respective HOX acids. During the phagocytosis of pathogens, MPO is released by azurophilic granules into phagolysosomes but can also be discharged outside phagocytes. Tissue damage that occurs during inflammation is largely due to MPO-derived oxidants. As referenced in previous chapters, this enzyme is a key factor in several conditions, including cardiovascular, inflammatory, neurodegenerative, renal, immune-mediated, and neurodegenerative diseases. Therefore, MPO is an attractive target for therapeutic

intervention in the prophylaxis of the aforementioned disorders. The only negative effect that can be expected from MPO inhibitors is a decrease in neutrophil activity against pathogens. MPO is an immunological enzyme that acts in neutrophils. However, MPO is located in azurophil granules, which protect this enzyme from changes in the extracellular environment. Therefore, it is believed that the effect of inhibitors on MPO activity can be easily attenuated by exclusively focusing on extracellular enzymes that are not critical for pathogen eradication but rather are involved in host damage.

Relatively polar MPO inhibitors cannot penetrate neutrophils and are thought to inhibit extracellular enzymes exclusively. The structure and reaction mechanism of MPO is known, allowing a rational strategy for the development of specific inhibitors, with the intention of preserving its activity against bacteria, but hindering its pathophysiological persistent activation during the course of the diseases [97].

There are three approaches to discover and develop such inhibitors:

The first approach is to prepare tiny compounds with a reduction potential of 0.97 V E°′ (A-/AH) 1.35 V. MPO compound I can easily oxidise these molecules, leading to the inactive state MPO compound II. At the same time, they cannot degrade the MPO compound II and cause this inactive form of MPO to build up. The main problem with these inhibitors is that when they are used in living organisms, several biomolecules can act as substrates for MPO and degrade the MPO compound II to restore the original enzyme. As a result, many inhibitors lose their efficacy in vivo.

The second approach focuses on tiny molecules that bind with high affinity to the active site of MPO. These chemicals are designed to strongly interact with the active site residues of the enzyme. The key amino acid that forms a salt bridge or hydrogen bond with the inhibitor is Glu102. In addition, to convert the MPO compound I into the MPO compound II, the inhibitor must have a reduction potential E°′ (A-/AH) of less than 1.35 V. When this type of molecule induces the inactive state of the enzyme, it maintains its contacts with the active site of MPO and prevents additional substrates from entering the active site, leading to the accumulation of MPO compound II by competitive inhibition. Several effective MPO inhibitors, such as aminoalkyl-indole compounds and aryl hydroxamic acid derivatives [98][99][100][101], were prepared using this strategy.

The third approach is to prepare tiny molecules that form covalent bonds after oxidation by MPO and have a relatively high affinity for the enzyme. These compounds are irreversible MPO inhibitors that act by degrading the heme group. Inhibitors that rely on overriding this mechanism are irreversible and form a strong covalent bond with the Fe of the haem centre, blocking the access of H_2O_2 to the active site, and thus inactivating the enzyme. The second mechanism is based on inducing competition between the inhibitor compound and the enzyme substrate. In this case, the inhibitor either forms a complex with MPO preventing further cycling or acts as a substrate for MPO by forming and accumulating compound II. An alternative approach based on the design of HOCl scavenging compounds can be considered in order to avoid the induced oxidative damage. However, this mechanism will not prevent the peroxidation cycle and the formation of superoxide and hydroxyl radical, which are involved in oxidative

stress and tissue injury. Due to the complexity of the MPO catalytic mechanism, the search for an effective inhibitor is still under development [102].

Lifestyle factors are important drivers of chronic diseases such as cardiovascular syndrome, with inflammation being a key factor. MPO is an inflammatory enzyme associated with obesity, hypertension, and heart failure, so its attenuation could have protective effects on multiple organs. Arnold Piek et al., 2019, tested the effects of a novel oral MPO inhibitor AZM198 in an obese/hypertensive mouse model with a cardiac phenotype Treated animals showed therapeutic AZM198 levels of 2.1 µM, corresponding to a 95% inhibition of MPO. AZM198 reduced elevated circulating MPO levels in HFD/AngII mice to normal values. Independently of food intake, body weight gain and fat accumulation were attenuated, along with reduction in visceral adipose tissue (VAT) inflammation and the attenuation of the severity of non-alcoholic steatohepatitis [103].

Most peroxidase enzymes are inhibited by benzoic acid hydrazide (BAH)-containing compounds, but the inhibition mechanism by BAH compounds is unknown. Jiansheng Huang et al., 2015, reported that the MPO inhibition by BAH and 4-(trifluoromethyl)-BAH due to hydrolysis of the ester bond between the MPO heavy chain glutamate 242 ((HC)Glu(242)) residue and the heme pyrrole A ring. In their manuscript, they provide evidence that the destruction of the heme ring does not occur by heme prosthetic group tracking and provides indications that the mechanism of hydrolysis follows a potential attack of the carbonyl of (HC)Glu(242), leading to a rearrangement that causes the release of the vinyl-sulphonium bond between (HC)Met(243) and the pyrrole A-ring [104].

Clinical studies have been only conducted on AZD5904, AZD3241, AZD4831, and PF06282999. The first three chemicals are thioxanthine derivatives, while the fourth is a thiopyrimidinone. The common mechanism of action of these drugs is a thioether bridge between the heme group of the enzyme and the oxidised thioxantine or thiopyrimidinone. Thioxanthins are compounds known as MPO inhibitors and derivatives with the 2-thioxanthin group show the highest activity. Thioxanthine is oxidised by compound I, forming a highly reactive free radical. This radical readily transfers electrons to the heme group of compound II and forms a covalent bond across the sulphur atom to one of the heme's pyrrole rings [105].

Several naturally occurring compounds possess inhibitory activities against MPO, including polyphenols, melatonin, and flavonoids. Seeds and aerial parts of *Peganum harmala* L. are widely used in Algeria as anti-inflammatory remedies. Sihem Bensalem et al. evaluated in their study the alkaloids and pure β-carboline compounds present, as well as their possible anti-inflammatory and MPO inhibitory action, concluding that the total alkaloids from seeds and aerial parts strongly inhibited MPO at 20 µg/mL (97 ± 5% and 43 ± 4%, respectively) while, at the same concentration, those from the roots showed very low inhibition (15 ± 6%) [106].

On the other hand, ceruloplasmin is a plasma protein produced by activated hepatocytes and macrophages and is involved in the physiological clearance and inactivation of MPO [107]. In addition to these, some naturally occurring compounds, such as polyphenols, with pronounced antioxidant and anti-inflammatory characteristics, have inhibitory activities against MPO. These compounds include ferulic acid, caffeic acid, resveratrol, chalcones, and gallic acid. [108][109]. Yuko Shiba et al., 2008, examined the MPO inhibitory effects of dietary flavonoids, using a

combination of biological assays and theoretical computational studies. Quercetin and the plasma metabolites inhibited the formation of dityrosine catalysed by the MPO enzyme and HL-60 cells in a dose-dependent manner [110].

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