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Original Article

# The inhibitory effects of plant extracts, vitamins and amino acids on myeloperoxidase activity

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**ABSTRACT**

**Background and Aims:** Myeloperoxidase (MPO, EC 1.11.2.2) is a vital antimicrobial enzyme, having a crucial role in host defense. Obstructing the activity of MPO is a possible pharmacological approach for the hindrance and management of a wide array of inflammatory illnesses. Consequently, blocking the activity of MPO is a potential pharmacological strategy for prevention and treatment of a broad range of inflammatory diseases.
**Methods:** In our study, inhibitory effects of 6 different sulfur containing plant extracts, 16 different vitamins and amino acids were studied for MPO inhibitory activities. The MPO enzyme activity was determined spectrophotometrically according to the method of Wei and Frankel.
**Results:** Among the aqueous plant extracts, black cabbage extract having $IC_{50}$=0.92±0.07 mM showed the highest inhibition. Among the vitamins and amino acids studied, the highest MPO enzyme inhibition was exhibited by ascorbic acid with $IC_{50}$=0.01±0.003 and cysteine with $IC_{50}$=1.09±0.73 mM.
**Conclusion:** Based on the outcomes, it was observed that all the examined plant extracts, vitamins and amino acids inhibited MPO enzyme at certain ratios.

**Keywords:** Myeloperoxidase, enzyme, inhibition, plant extract, vitamins, amino acids

## INTRODUCTION

Myeloperoxidase (MPO, EC 1.11.2.2) is a lysosomal hemoprotein found in the azurophilic granules in neutrophils (Unubol et al., 2015). Compared to neutrophils, the human monocytes have fewer MPO-positive granules which are lost into tissue macrophages during differentiation (Malle, Furtmüller, Sattler, & Obinger, 2007).

In the presence of $H_2O_2$, $Cl^-$ is oxidized to HOCl by MPO. It also functions as classic peroxidase, thereby producing a series of free radicals and reactive oxygen species (ROS). The inhibitors of MPO have high potentials for the treatment of many inflammatory diseases (Wurtz et al., 2018; Regasini et al., 2008). While many compounds (e.g. azides, anilines, phenols, hydrazides, and hydroxamic acids) are potent inhibitors of MPO activity in vitro, (Wurtz et al., 2018; van der Veen, de Winther, & Heeringa, 2009; Forbes et al., 2013) they are essentially toxic, consequently inappropriate for use as therapeutic agents (Tian, Ding, Peng, & Lu, 2017). For these reasons, researchers are constantly in search of new natural medications.

This study was aimed at examining the inhibitory activities of 6 sulfur containing plant extracts, as well as 16 different vitamins and amino acids on MPO enzyme.

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## MATERIALS AND METHODS

### Chemicals

All reagents used in the inhibition of MPO enzyme activity were of analytical grade and commercially available.

### Preparation of aqueous plant extracts and other drugs

Plant materials were washed with water and dried at room temperature. Dried plants (20 g) were extracted by adding 200 mL of distilled water and refluxed for 8 hours. The extracts were then filtered and the filtrates were taken to the pre-weighed glass flasks. The glass flasks were placed in a rotary evaporator and the water of the mixtures was evaporated under reduced pressure. Then, extracts were kept in Eppendorf tubes at -20°C. Before use, all extracts were dissolved in distilled water at different concentrations. Also, vitamins, amino acids and peptides were prepared by being dissolved in distilled water.

### Enzyme inhibitory activity assay

Rat gastric tissues homogenates were used as the enzyme source. The gastric tissues were homogenized in 0.9% saline to make up a 10% (w/v) homogenate. The homogenate was centrifuged at 3000 rpm for 30 minutes at 4°C and the supernatant was used for enzyme inhibition experiments.

MPO enzyme inhibitory activity was determined spectrophotometrically according to Wei and Frenkel's method (Wei & Frenkel, 1991). In a test tube, 1.3 mL of 4-aminoantipyrine (25 mM in 2% phenol) and 1.5 mL hydrogen peroxide solutions (1.7 mM) was shaked for 4 min, and 0.1 mL inhibition solution were added and stirred. The reaction was started by adding 0.2 mL of homogenate. Then, the change in absorbance was measured at 510 nm for 5 min. Reference measurements were performed without inhibitors (control value). Quercetin was used as standard.

The potent inhibition of MPO activity was calculated as follows:

$$\text{MPO Inhibition (\%)} = \frac{(A-B)}{A} \times 100$$

A is the enzyme activity without inhibitor. B is the activity in presence of inhibitor. The $IC_{50}$ was determined as the concentration of plant extract required to inhibit MPO activity by 50%. The results are given as half maximal inhibitory concentrations ($IC_{50}$) values calculated from the regression equations prepared from the concentrations of the samples. Low $IC_{50}$ values indicate higher enzyme inhibitory activity.

## RESULTS

MPO inhibition values of different sulfur containing plant extracts are given in Table 1. High MPO inhibitory action correlates to a low $IC_{50}$ value. Decreased inhibition values of plant extracts according to the lowest $IC_{50}$ values are as follows: black cabbage > quercetin > white cabbage > purple cabbage > onion > brussels sprouts > cauliflower. As observed from the results, black cabbage ($IC_{50}$=0.92 ± 0.07 mg/mL) and white cabbage ($IC_{50}$=8.64 ± 0.98 mg/mL) displayed the highest MPO inhibitory effects when compared to other species and onion extracts (Table 1).

**Table 1. The inhibition of myeloperoxidase activity by various plant extracts.**

| Plant extracts | Concentration (mg/mL) | Inhibition (%)* | $IC_{50}$ Value (mg/mL)* |
|---|---|---|---|
| Black cabbage | 0.25 | 13.2±4.17 | 0.92±0.07 |
| | 0.5 | 29.2±5.45 | |
| | 1.0 | 54.2±4.74 | |
| Brussels sprouts | 25 | 16.3±3.39 | 95.04±1.43 |
| | 50 | 36.3±5.59 | |
| | 100 | 50.2±0.85 | |
| Cauliflower | 25 | 6.3±2.05 | 131.13±3.68 |
| | 50 | 11.6±2.83 | |
| | 100 | 37.7±0.64 | |
| Onion | 1.25 | 5.0±1.98 | 24.09±7.71 |
| | 2.5 | 6.1±2.47 | |
| | 5.0 | 12.7±5.23 | |
| Purple cabbage | 1.25 | 4.6±2.90 | 23.96±9.61 |
| | 2.5 | 8.2±1.13 | |
| | 5.0 | 13.2±2.19 | |
| White cabbage | 0.2 | 6.0±0.00 | 8.64±0.98 |
| | 0.5 | 14.5±4.95 | |
| | 2.0 | 23.3±4.88 | |
| | 5.0 | 31.5±4.24 | |
| Quercetin | 0.2 | 37.36±2.64 | 1.49±0.17 |
| | 0.3 | 43.68±2.63 | |
| | 0.6 | 56.32±8.67 | |
| | 1.0 | 70.69±3.45 | |

*Mean ± SD

The inhibitory effects of vitamins are shown in Table 2. All the tested compounds exhibited MPO inhibitory activity. Ascorbic acid was found to be the most effective MPO inhibitory agent among the vitamins, its $IC_{50}$ value was 0.01 ± 0.003 mg/mL (Table 2). Decreased inhibition values of vitamins to the lowest $IC_{50}$ values are as follows: ascorbic acid > DL-α-tocopherol > quercetin > lipoic acid > pyridoxal-5 as-phosphate > DL-methionine methyl sulfonium chloride > nicotinamide > β carotene > routine hydrate > riboflavin > anorine hydrochloride.

According to Table 3, the amino acid with the lowest $IC_{50}$ value was L-cysteine. Cysteine was found to have the most effective MPO inhibitory activity among the amino acids, with an $IC_{50}$ value of 1.09 ± 0.73 mg/mL (Table 3). The highest inhibition values of the peptides and amino acids are as follows: L-cysteine > reduced glutathione > quercetin > L-lysine > L-glutamic acid > L-methionine > L-alanine.

## DISCUSSION

MPO is a heme enzyme which uses $H_2O_2$ and $Cl^-$ to catalyse the production of the reactive and cytotoxic oxidant hypochlorous acid (HOCl) (Daugherty, Dunn, Rateri, & Heinecke, 1994). The initial product of the MPO $H_2O_2$-$Cl^-$ system is the potent antimicrobial oxidant hypochlorous acid/hypochlorite (HOCl/$OCl^-$). However, under pathological conditions, persistent activation of the MPO-$H_2O_2$ system of activated phagocytes may adversely affect tissues. HOCl is able to initiate modification reactions targeting lipids, DNA and (lipo)proteins, including halogenation, nitration and oxidative cross-linking (Malle et al., 2007). Also, MPO – mediated damage is involved in the pathogenesis of several inflammatory conditions, atherosclerosis, demyelinating diseases of the central nervous system and some tumors (Unubol et al., 2015).

As a result of systematic studies, plants have been used in modern medicine, phytotherapy and pharmacy according to

**Table 2. The inhibition of myeloperoxidase by vitamins.**

| Plant extracts | Concentration (mg/mL) | Inhibition (%)* | $IC_{50}$ Value (mg/mL)* |
|---|---|---|---|
| Anorine hydrochlorid | 2.5 | 5.8±2.19 | 40.86±5.05 |
| | 5.0 | 9.8±2.90 | |
| | 10.0 | 14.4±3.25 | |
| Ascorbic acid | 2.5 | 68.6±8.06 | 0.01±0.003 |
| | 5.0 | 83.8±3.82 | |
| | 10.0 | 91.5±1.77 | |
| β-carotene | 1.0 | 7.9±0.99 | 12.85±1.12 |
| | 2.5 | 12.2±1.91 | |
| | 5.0 | 22.2±2.47 | |
| (±)-α-Lipoic acid | 0.3 | 2.3±0.49 | 5.05±0.22 |
| | 0.5 | 9.9±2.62 | |
| | 1.0 | 10.5±0.42 | |
| DL-methionine methylsulfonium chloride | 0.5 | 7.0±1.13 | 8.31±2.18 |
| | 1.0 | 8.7±2.90 | |
| | 2.5 | 18.3±5.44 | |
| Nicotinamide | 1.0 | 6.5±2.05 | 11.54±3.07 |
| | 2.5 | 12.9±2.05 | |
| | 5.0 | 24.0±5.66 | |
| Pyridoxal-5'-phosphate | 0.5 | 4.2±2.89 | 7.20±1.17 |
| | 1.0 | 4.7±0.89 | |
| | 2.5 | 17.8±1.51 | |
| Riboflavin | 1.0 | 4.8±1.56 | 16.14±7.17 |
| | 2.5 | 8.7±1.13 | |
| | 5.0 | 30.8±0.50 | |
| Routine hydrate | 2.5 | 31.3±1.77 | 13.00±2.67 |
| | 5.0 | 38.9±0.78 | |
| | 10.0 | 43.3±2.97 | |
| DL-α-tocopherol acetate | 2.5 | 5.3±3.75 | 0.03±0.01 |
| | 5.0 | 8.6±4.03 | |
| | 10.0 | 19.5±6.93 | |
| Quercetin | 0.5 | 37.36±2.64 | 1.49±0.17 |
| | 1.0 | 43.68±2.63 | |
| | 2.0 | 56.32±8.67 | |
| | 3.0 | 70.69±3.45 | |

*Mean±SD

**Table 3. The inhibition of myeloperoxidase by amino acids and peptides.**

| Plant extracts | Concentration (mg/mL) | Inhibition (%)* | $IC_{50}$ Value (mg/mL)* |
|---|---|---|---|
| L-Alanine | 10.0 | 3.0±1.77 | 215.99±55.54 |
| | 25.0 | 5.6±1.20 | |
| | 50.0 | 12.5±2.26 | |
| L-Cysteine | 5.0 | 59.4±3.25 | 1.09±0.73 |
| | 10.0 | 85.3±1.20 | |
| | 20.0 | 98.8±0.57 | |
| L-Glutamic acid | 10.0 | 14.3±5.16 | 57.73±2.71 |
| | 25.0 | 29.1±1.20 | |
| | 50.0 | 43.7±0.71 | |
| L-Lysine | 2.5 | 3.0±0.85 | 54.91±19.41 |
| | 5.0 | 6.2±0.00 | |
| | 10.0 | 10.4±4.03 | |
| L-Methionine | 5.0 | 2.3±1.41 | 83.80±17.19 |
| | 10.0 | 5.6±2.33 | |
| | 20.0 | 11.6±1.84 | |
| Reduced glutathione (GSH) | 5.0 | 33.4±0.49 | 7.43±0.32 |
| | 10.0 | 71.8±2.05 | |
| | 20.0 | 92.3±0.42 | |
| Quercetin | 0.5 | 37.36±2.64 | 1.49±0.17 |
| | 1.0 | 43.68±2.63 | |
| | 2.0 | 56.32±8.67 | |
| | 3.0 | 70.69±3.45 | |

*Mean±SD

the effects of secondary metabolites and their composition. The use of synthetic drugs in general provides an effective and rapid treatment. But in some cases, high dose intake causes various side effects on the organism and systems. Thus, the use of herbal medicines or their active components represents alternatives for the treatment of numerous inflammatory disease (Castro, Ocampo & Franco, 2014). Some food derived polyphenols flavonoids and phenolic antioxidants have inhibitory effects on MPO (Kato, Nagao, Terao, & Osawa, 2003 ). Many studies demonstrate that extracts of different parts of various plant species such as *Peganum harmala* (Bensalem et al., 2014), *Ginkgo biloba* (Tian et al., 2015) *Careya arborea* (Begum, Sharma, Pillai, Aeri, & Sheliya, 2015), *Tragopogon graminifolius* (Farzaei et al., 2015), *Costus igneus* (Krishnan, Mathew & Vijayalakshmi 2014), *Urera aurantiaca* (Riedel, Marrassini, Anesini, & Gorzalczany, 2015) *Arctium lappa* (Wu et al., 2014) *Punica granatum* (Bachoual, Talmoudi, Boussetta, Braut, & El-Benna, 2011), *Onosma armeniacum* (Cadirci, Suleyman, & Aksoy, 2007), *Vaccinium corymbosum* (Torri et al., 2007), *Mangifera indica* (Garrido, González, Lemus, Delporte, & Delgado, 2006) and *Iberis amara* L. (Schempp, Hippeli, Weiser, Kelber, & Elstner, 2004) have shown significant effects on MPO enzyme inhibition.

Studies on cabbage species have shown that they contain flavonoids, ascorbic acid, DL-α-tocopherol acetate and DL-methionine methyl sulfonium chloride (vitamin U) (Podsędek, 2007; Sokmen, Tunali, & Yanardag, 2012). Podsedek (2007) reported that the vitamin C level of Brassica vegetables considerably differ among and within their subspecies. As observed from the results of this study, black and white cabbage exhibited the highest inhibitory activities at the concentration of 1 mg/mL (54.2±4.74%) and 5 mg/mL (31.5±4.24%), respectively on MPO enzyme activity. These inhibition values are thought to be caused by significant amounts of ascorbic acid, carotenoids, DL-α-tocopherol acetate and phenolic compounds in black cabbage and white cabbage. Many studies reported that flavonoids and polyphenols in natural extracts inhibit MPO at micromolar concentrations (Regasini et al., 2008; Kostálová, Mísíková, & Gáborová, 2001), and most of them are competitive substrates for MPO, through the production of HOCl and other hypohalides (Sokmen, Tunali, & Yanardag, 2012).

Ascorbic acid is a hydrophilic compound and acts directly by scavenging lipid hydroperoxide, superoxide and hydroxyl radicals, or indirectly by playing an important role in recycling tocopherol, a process that results in the conversion of ascorbic acid into a semiascorbyl radical (Bursać-Mitrović et al., 2016). In this study, ascorbic acid was found as having the most effective MPO inhibitory activity among the vitamins, its $IC_{50}$ value was 0.01±0.003 mg/mL. Black cabbage contains considerably high levels of ascorbic acid.

L-Cysteine is an amino acid containing the sulfhydryl group that has a critical role in preventing oxidative stress in cells. In our study, cysteine was found to have the most effective MPO inhibitory activity among the amino acids, with an $IC_{50}$ value of 1.09±0.73 mg/mL . Sagone et al. (1989) demonstrated that a sulfur centered compound - dimethylthiourea inhibited the

MPO enzyme by blocking the formation of HOCl, and can also react with $H_2O_2$ in certain experimental systems (Sagone Jr., Husney, Wewers, Herzyk, & Davis, 1989). On the other hand, sulfides were found to exhibit protective effects against several pathological diseases. Pálinkás et al., (2015) and Garai et al., (2017) suggested that this effect is possibly due to the obstruction of MPO-mediated oxidant production and/or synthesis of sulfane sulfur (via MPO catalysed sulfide oxidation by neutrofil-produced $H_2O_2$) (Garai et al., 2017).

## CONCLUSION

The results of this study indicate that sulfur containing plant extracts, vitamins and amino acids are effective inhibitors of MPO activity. It may be suggested that these compounds and the plant extracts serve as alternative and complementary treatments in regulating immune responses in inflammatory regions when appropriate concentrations are added to a controlled diet.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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