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In Vitro Inhibitory Effects of Some Antiviral, Antidiabetic, and Non-Steroidal Anti-Inflammatory Drug Active Compounds on *α*-Glucosidase and Myeloperoxidase Activities

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Abstract: In recent decades, interest in enzyme inhibition, such as myeloperoxidase (MPO) and glycosidases, has dramatically increased, mainly because these enzymes play a vital role in many biological processes. Based on the biological potential associated with these enzymes, instead of several glycosidase and myeloperoxidase (MPO) inhibitors that have been developed, there are not enough studies on the inhibition effects of widely used types of antivirals (aciclovir, tenofovir), oral antidiabetics (glibenclamide, glibornuride, glurenorm, metformin), and non-steroidal anti-inflammatory drugs (NSAIDs) active substances (benzydamine HCl, diclofenac, indomethacin, ketorolac tromethamine, paracetamol, salicylic acid) today. For that reason, the aim of our study is to investigate the inhibition effects of these 12 different drug active substances on α-glucosidase and MPO activities. According to the obtained results, the screened drug active substances acyclovir, glibornuride, and paracetamol inhibited *α*-glucosidase with the lowest IC_{50} value, while similarly low values for MPO were found by tenofavir, glurenorm, and indomethacin. In our study, we can suggest that these active pharmaceutical ingredients may contribute to the pharmaceutical industry due to their inhibitory effects on α-glucosidase and MPO *in vitro*.

Keywords: *α*-Glucosidase, myeloperoxidase, enzyme inhibition, drug active compounds.

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1. INTRODUCTION

Enzyme inhibitors are key molecules that regulate the velocity of enzymatic reactions in metabolism. A possible correlation between enzyme activity and diseases is an important reason for increasing interest in inhibition research. Examination of different antiviral, antidiabetic, and nonsteroidal anti-inflammatory drug (NSAIDs) active compounds demonstrated their inhibitory effect on the two important enzymes *α*-glycosidase and myeloperoxidase (MPO).

Glycosidases are enzymes responsible for the hydrolysis of glycosidic bonds in glycoconjugates, that are found in almost all living organisms (1). Today, wide structural diversity of carbohydrates, stable character of glycosidic bonds and catalytic rates of up to 10^{17} times have led to increased interest in glycosidases (2). Although catalysis of carbohydrates by these enzymes is biologically common, glycosidases also take part in various intracellular functions, such as the formation of signaling molecules or glycoconjugate catabolism (3).

Since glycosidases are enzymes responsible for the breakdown of di-, oligo- and polysaccharides and glycoconjugates, they appear in every aspect of life. Inhibition of starch hydrolysis to slow down the absorption of glucose in starchy foods is an effective way to prevent type 2 diabetes. Recently, glycosidase inhibitors, synthesized or isolated from various plant sources, are used for several purposes, such as elucidating the mechanisms catalyzed by various types of glycosidases, in addition to being used in treatments (4). Besides being involved in the digestion of carbohydrates in the intestines,

glycosidases are involved in many biochemical processes, such as the catabolization of glycoconjugates in lysosomes and the processing of glycoproteins through post-translational modifications. Glycosidase inhibitors are important both in understanding the biological functions of glycoproteins and in investigating the structures and reaction mechanisms of glycosidases (5).

Myeloperoxidase (MPO) is an inflammatory enzyme that triggers both oxidative stress and neuroinflammation in damage resulting from pathological processes such as cerebral ischemia-reperfusion and is also a therapeutic target (6). MPO is one of the major proteins of the antimicrobial system in mammalian neutrophils (7). Since the surface of MPO molecule contains numerous lysine and arginine residues, which make the MPO a highly cationic molecule (PI~10), the interaction of MPO with a multitude of compounds or cells that have a negatively charged surface (or domain) including bacterial cells (8), endothelial cells (9), extracellular matrix components, particularly polyanionic glycosaminoglycans (9), apolipoprotein B-100 (10) and apolipoprotein A-I (11), albumin (12), cytokeratin I (13), α1-antitrypsin (14) and ceruloplasmin (15). It is reported that in physiological conditions, when MPO is binding to endothelial cells and glycosaminoglycans, it is inhibited by heparin and the multi-functional copper containing protein ceruloplasmin, which may be explained these molecules as anti-inflammatory (16, 17).

Apart from infiltrated neutrophils, MPO is also located in activated microglial cells, astrocytes, and neurons in the ischemic brain. Activation of MPO can catalyze the reaction of chloride and H_2O_2 to produce HOCl. Induced MPO activity in tissues also causes the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), activation of polarization and inflammation-related signaling pathways in microglia and neutrophils, and consequent oxidative stress. Therefore, inhibition of MPO may also be therapeutically targeted for ischemic stroke and attenuation of neuroinflammation. It has been observed that targeting MPO both at the genetic expression level and in terms of catalytic inhibition is important in reducing possible neurological problems and brain infarction (6).

In this paper, we investigate the inhibitory effect of 12 different drug active substances on *α*-glucosidase and MPO activities *in vitro*. Moreover, in addition to the antiviral, blood glucose lowering and anti-inflammatory effects of these drug active ingredients, which are already widely used, we also aimed to emphasize to what extent they have the potential to inhibit these two enzymes.

2. EXPERIMENTAL SECTION

2.1. Inhibition of *α*-glucosidase

α-Glucosidase inhibition assay was performed according to the method of Tao et al. (18). 5 µL of different concentrations of inhibitory solution and 20 µL of 0.15 U/mL enzyme solution were added to 75 µL of 0.1 M phosphate buffer (pH 7.4) and mixed. In the control sample, 5 µL of dimethyl sulfoxide (DMSO) were taken instead of the inhibitor solution. The same amount of DMSO and buffer was added to the blind instead of the inhibitor and enzyme solutions, and the same amount of buffer solutions were added to the color-blind instead of the enzyme. After 10 minutes of incubation at 37 °C, 20 µL of 0.005 M *p*-nitrophenylglycopyranoside (PNG) was added to all samples and the absorbance values at 410 nm were read. Acarbose was used as a positive control. The inhibition (%) values were calculated with the help of the following formula.

α-Glucosidase Inhibition (%) = ([A-B]/A) ×100

A: The absorbance value of the control solution in the spectrophotometer.
B: The absorbance value of the solution containing the sample in the spectrophotometer.

2.2. Inhibition of MPO

Rat gastric tissue 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 (19). In a test tube, 1.3 mL of 4-aminoantipyrine (25 mM in 2% phenol) and 1.5 mL of hydrogen peroxide solutions (1.7 mM) were shaken 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). Rutin hydrate was used as a standard. The potent inhibition of MPO activity (%) was calculated as follows:

MPO Inhibition (%) = (A-B)/A x 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 drug active compound required to inhibit *α*-glucosidase and MPO activities by 50%. The results are given as half maximal inhibitory concentrations (IC_{50}), whose value could be used to assess the inhibitory efficiency of the inhibitor calculated from the regression equations prepared from the concentrations of the samples. All measurements were done in triplicate. The percentage of inhibition was calculated from the residual activity in comparison to the control sample. Low IC_{50} values indicate higher enzyme inhibitory activity.

3. RESULTS AND DISCUSSION

The inhibitory effects of antiviral drug active compounds and standard compounds on *α*-glucosidase and MPO are given in Table 1.

Table 1: *α*-Glucosidase and MPO inhibitory activities of antiviral drug active compounds at different concentrations.

Enzyme	Drug active compounds	Drug active compounds conc. (mg/mL)	Inhibition (%) *	IC_{50} (mM)*
α-Glucosidase	Acyclovir	10.0 15.0 25.0	12.25±1.61 19.81±2.73 25.21±2.67	58.41±16.73
	Tenofovir	0.5 5.0 50.0	10.96±3.19 17.89±1.66 23.53±1.51	204.40±30.29
	Acarbose	2.0 5.0 7.5	21.83±0.65 26.77±2.77 40.20±1.77	10.57±0.57
MPO	Acyclovir	10.0 15.0 20.0	5.8±2.40 6.0±0.57 6.6±1.06	321.03±214.03
	Tenofovir	10.0 25.0 50.0	16.7±2.90 31.2±2.62 47.1±0.57	52.90±0.68
	Rutin hydrate	2.5 5.0 10.0	31.3±1.77 38.9±0.78 43.3±2.97	13.00±2.67

*Mean±SD

The studied two antiviral drug active compounds, acyclovir and tenofovir, have shown inhibitory effects on both *α*-glucosidase (IC_{50}= 58.41±16.73 mM for acyclovir and 204.40±30.29 for tenofovir) and MPO (IC_{50}= 321.03±214.03 mM for acyclovir and 52.90±0.68 for tenofovir) when compared to standard drugs acarbose and rutin hydrate (IC_{50}=10.57±0.57 for *α*-glucosidase; IC_{50}=13.00±2.67 for MPO). According to Table 1, acyclovir is a more potent inhibitor on *α*-glucosidase than MPO, while tenofavir inhibits MPO more effectively. The inhibitory effects of antiviral drug active compounds and standard on *α*-glucosidase decreased activity are in the following order: acarbose > acyclovir > tenofovir. Similarly, for MPO, this order is as follows: rutin hydrate > tenofovir > acyclovir.

The inhibitory effects of antidiabetic drug active compounds and standard compounds on *α*-glucosidase and MPO are given in Table 2.

According to Table 2, glibornuride and glurenorm showed the lowest IC_{50} values for *α*-glucosidase (IC_{50}=0.29±0.04) and MPO (IC_{50}=4.11±0.26), respectively. Both enzymes were inhibited at the lowest rate by metformin (IC_{50}=142.59±46.64 for *α*-glucosidase; IC_{50}=151.05±149.81 for MPO). The highest inhibition values of the antidiabetic drug active compounds and standards for *α*-glucosidase are as follows: glibornuride > glurenorm > glibenclamide > acarbose > metformin; and for MPO, glurenorm > rutin hydrate > glibenclamide > glibornuride > metformin, respectively (Table 2).

α-Glucosidase and MPO inhibitory activities of NSAIDs compounds and standard compounds are given in Table 3.

Among NSAIDs, paracetamol was found to be the most potent *α*-glucosidase enzyme inhibitor (IC_{50}=4.02±0.20), while salicylic acid was identified as the weakest *α*-glucosidase enzyme inhibitor (IC_{50}=206.23±15.28). While indomethacin did not show any inhibitory effect on *α*-glucosidase, on the contrary, it was found to strongly inhibit MPO at the highest rate ($IC_{50}=3.3x10^{-5} \pm 0.03x10^{-5}$). Inhibition rate of NSAIDs and standard compounds, for *α*-glycosidase is: paracetamol > acarbose > ketorolac > diclofenac > benzidamine HCl > salicylic acid; and for MPO is indomethacin > diclofenac > paracetamol > rutin hydrate > ketorolac tromethamine > salicylic acid > benzidamine HCl, respectively.

Given their multitude of roles *in-vivo*, inhibition of *α*-glucosidase and MPO in a number of different processes is very important. *α*-Glucosidase inhibition has potential in the treatment of lysosomal storage diseases, diabetes, and viral infections, including influenza and HIV. On the other hand, suppressing the catalytic activity of MPO prevents the accumulation of reactive oxygen species that cause tissue damage in some inflammatory diseases such as rheumatoid arthritis, atherosclerosis, multiple sclerosis, and cerebral ischemia-reperfusion. (6,20). Therefore, MPO and its downstream inflammatory pathways might be attractive targets for both prognostic and therapeutic intervention in the prophylaxis of all mentioned illnesses. Besides that, *α*-glucosidase inhibitors can play an important role in controlling the postprandial blood glucose levels of diabetics and keeping the blood glucose levels in a suitable range by delaying the digestion of carbohydrates and diminishing the absorption of

monosaccharides (21-23).

In recent years, in addition to different sugar-based inhibitory molecules being designed (24), extracts obtained from different parts of various plants have also been reported to exhibit inhibitory activity against glucosidase (25-27). Most of the *α*-glucosidase inhibitors in these plants are secondary metabolites such as alkaloids, phenolic acids, flavonoids, terpenoids, anthocyanins, and their glycosides, and these have been suggested to have much stronger inhibitory potentials than the inhibitory effect obtained from acarbose (28).

Among the antiviral agents, acyclovir is used in the treatment of diseases such as herpes viruses, genital herpes, chickenpox, shingles, and dermal infections. Instead of this, in the studies conducted with various antiviral drugs for the prevention of the SARS CoV-2 pandemic, two antiviral drugs, muglistat and catastanospermine (the prodrug of celgosivir) are used for the inhibition of *α*-glucosidase (I and II) involved in the early stages of glycoprotein N-linked oligosaccharide processing in the endoplasmic reticulum (ER) where acyclovir inhibition is not examined (29, 30). On the other hand, another antiviral drug, tenofovir, is available for the treatment of HIV and HBV infections (31). No previous studies were found based on *in vitro* inhibition of *α*-glucosidase and MPO by acyclovir and tenofovir. However, Olojede et al., (2022) demonstrated in their research that tenofovir disoproxil fumarate loaded on silver nanoparticles successfully reduced the blood sugar level of diabetic rats through the inhibition of *α*-glycosidase and *α*-amylase in the gastrointestinal tract *in vivo*. (32). In our study, we have found that acyclovir inhibited *α*-glucosidase more effectively than tenofovir, with an inhibition rate of IC_{50}=58.41±16.73 mM. On the other hand, tenofovir reduced MPO activity more effectively (IC_{50}=52.90±0.68 mM) than acyclovir (IC_{50}=321.03±214.03 mM).

α-Glucosidase inhibitors are oral antihyperglycemic drugs that inhibit upper gastrointestinal enzymes that break down complex carbohydrates into glucose. Most conventional glycosidase inhibitors mimic the structures of monosaccharides or oligosaccharides and are well accepted by organisms. As a result, the absorption of glucose is delayed, postprandial glucose is reduced, and glycemic control is improved (33). Widely used two types of oral antidiabetics in the treatment of hyperglycemia are biguanides (metformin) and the second generation of sulphonylureas (glibenclamide, glibornuride, and gliquidon (glurenorm)).

Table 2: *α*-Glucosidase and MPO inhibitory activities of antidiabetic drug active compounds at different concentrations.

Enzyme	**Drug active compounds**	**Drug active compounds conc. (mg/mL)**	**Inhibition (%)***	**IC_{50} (mM)***
α-Glucosidase	Glibenclamide	0.05 0.25 0.50	8.52±0.78 11.21±1.96 14.20±3.40	4.60±3.50
	Glibornuride	0.001 0.01 0.1	2.24±0.77 13.15±0.68 21.53±2.33	0.29±0.04
	Glurenorm	0.1 0.5 0.75	20.33±1.30 29.02±2.02 49.03±1.44	0.86±0.05
	Metformin	10.0 25.0 50.0	10.17±4.04 12.85±1.58 23.32±3.59	142.59±46.64
	Acarbose	2.0 5.0 7.5	21.83±0.65 26.77±2.77 40.20±1.77	10.57±0.57
MPO	Glibenclamide	2.5 5.0 10.0	4.5±3.18 7.3±1.98 12.1±0.21	48.7±9.93
	Glibornuride	5.0 12.5 25.0	5.3±0.78 7.4±2.33 13.8±2.83	119.85±34.86
	Glurenorm	$2.5x10^{-1}$ 0.5 1.0	1.1±0.71 3.3±0.71 10.5±1.27	4.11±0.26
	Metformin	2.5 5.0 10.0	3.7±3.39 6.0±2.47 8.2±2.19	151.05±149.81

	Rutin hydrate	2.5 5.0 10.0	31.3±1.77 38.9±0.78 43.3±2.97	13.00±2.67

*Mean±SD

Table 3: *α*-Glucosidase and MPO inhibitory activities of NSAIDs compounds at different concentrations.

Enzyme	**Drug active compounds**	**Drug active compounds conc. (mg/mL)**	**Inhibition (%)***	**IC_{50} (mM)***
α-Glucosidase	Benzydamine HCl	50 60 70	23.09±1.01 33.75±3.26 46.85±2.27	73.19±2.16
	Diclofenac	15 25 45	8.33±0.57 24.51±1.35 41.20±1.02	52.30±1.21
	Indomethacin	-	-	-
	Ketorolac-tromethamine	2.5 10 15	26.13±0.58 30.70±0.35 43.20±2.72	22.56±1.92
	Paracetamol	0.1 1.0 5.0	16.1±1.40 39.1±0.48 54.9±1.70	4.02±0.20
	Salicylic acid	25 40 100	3.31±0.80 6.43±3.08 22.39±1.66	206.23±15.28
	Acarbose	2.0 5.0 7.5	21.83±0.65 26.77±2.77 40.20±1.77	10.57±0.57
MPO	Benzydamine HCl	2.5 5.0 10.0	2.7±2.83 3.5±0.99 5.3±2.69	153.17±102.15
	Diclofenac	$3.4x10^{-3}$ $5.1x10^{-3}$ $8.4x10^{-3}$	19.4±11.81 44.5±2.05 85.9±4.03	$5.6x10^{-3}$±0.0003
	Indomethacin	$2.8x10^{-8}$ $2.8x10^{-6}$ $1.4x10^{-5}$	18.5±2.12 20.3±2.33 41.6±21.4	$3.3x10^{-5}$±$0.03x10^{-5}$
	Ketorolac-tromethamine	1.25 2.5 5.0	3.3±2.97 9.4±1.34 11.3±3.04	24.92±2.74
	Paracetamol	$6.6x10^{-3}$ $9.9x10^{-3}$ $1.7x10^{-2}$	1.3±0.14 19.7±11.6 22.3±3.54	0.032±0.004
	Salicylic acid	5.0 10.0 20.0	5.4±2.05 6.8±0.07 13.7±2.26	83.69±5.64
	Rutin hydrate	2.5 5.0 10.0	31.3±1.77 38.9±0.78 43.3±2.97	13.00±2.67

*Mean±SD

Especially, sulfonylureas are widely used in medicine as potent blood glucose-reducing agents for the treatment of diabetes. Sulfonylureas alter the plasma membrane of cells to increase their responsiveness to insulin action, by increasing the number of insulin receptors (34). Today, a wide variety of sulfonylurea derivatives continue to be synthesized and recommended as adjunctive agents in treatments to reduce diabetes symptoms. Although it has been emphasized that the mechanism of action of sulfonylureas in diabetes is on insulin secretion in the pancreas., Bui et al., (2021) demonstrated in their research that different new synthesized sulfonylurea derivatives exhibited significant *α*-glucosidase

inhibition compared to commercially available acarbose and glipizide (35). Similarly, in our study, we found that glubornuride and glurenorm, also inhibited *α*-glucosidase more strongly than acarbose (IC_{50}= 0.29±0.04 mM; IC_{50}= 0.86±0.05 mM). On the other hand, when examined with various diabetes models after the formation of diabetes, it is observed that MPO activity clearly increases in various diabetic tissues (36-38). Although, a broad and chemically heterogeneous group of molecules (alkylindoles, fluoroindoles, indazonoles, dapsone, bis-arylalkamines, nitroxides, and phenolic compounds) have been found to successfully inhibit MPO, no data were found regarding *in vitro* inhibition with oral antihyperglycemic drugs (39). Our research showed that each examined antihyperglycemic drug in Table 2 inhibited MPO at different rates, but the highest inhibition was observed to be achieved by glurenorm (IC_{50}= 4.11±0.26 mM). However, if we need to make a comparison between both groups, it was found that sulfonylurea group oral antidiabetic agents are more effective inhibitors of both studied enzymes, *α*-glucosidase and MPO, than metformin, which is a biguanide type.

The NSAIDs are among the most widely prescribed drugs worldwide (40), and these components were investigated for their ability to affect the chlorinating activity of human MPO and to scavenge HOCl, which is the main MPO system product (41). In our study, although NSAIDs showed an inhibitory effect on the *α*-glucosidase, it was observed that this effect was actually more effective on MPO. Moreover, indomethacin was found to be the strongest MPO inhibitor with the lowest IC_{50} value (IC_{50}= $3.3x10^{-5}$ ±$0.03x10^{-5}$), whereas on *α*-glucosidase, it was observed to be unaffected (Table 3). Supporting this, in an *in-vitro* study using murine neutrophils, it was found that indomethacin and NSIDs inhibited HOCl formation in MPO (42). Similarly, Zuurbier et al., (1990) demonstrated that, in isolated MPO from human polymorphonuclear neutrophils, diclofenac inhibited the enzyme during the reaction cycle of MPO with H_2O_2 (43). Supporting these findings, we also found in our study that diclofenac inhibits MPO very effectively. (IC_{50}= $5.6x10^{-3}$ ± 0.0003 mM).

4. CONCLUSION

Despite the discovery of different novel *α*-glucosidase and MPO inhibitors as potential novel therapeutic interventions for many diseases, in existing literature there is a lack of information about the inhibitory effects of 12 commonly used drug active compounds studied in our research. Among the scanned different antiviral, antidiabetic, and NSAIDs active compounds, it was found that these selected ingredients are effective inhibitiors of *α*-glucosidase as well as MPO *in-vitro,* except indomethacin, which is not effective on *α*-glucosidase activity in contrast to MPO. Therefore, we can suggest that these drugs, which are used as antidiabetics, antivirals, and NAIDs in the field of health, can contribute to the pharmaceutical industry due to their *α*-glycosidase and MPO inhibition effects.

5. CONFLICT OF INTEREST

There are no conflicts to declare.

6. ACKNOWLEDGMENTS

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