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Inhibitory Effect of Meropenem Antibiotic on the Activity of Glutathione-S-Transferases

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ABSTRACT: The following experiment investigated the effect of meropenem antibiotic on the activity of glutathione-S-transferase (GST) isoenzymes. This effect was estimated spectrophotometrically at different concentrations of meropenem using 1-chloro-2,4-dinitrobenzene (CDNB) as a substrate. The obtained results revealed that meropenem antibiotic demonstrated an inhibitory effect on GST activity at low tested concentrations (0.25, 0.5, 1 and 2.5 mM) that resulted in 30.5, 39.4, 45.1, and 100% inhibition, respectively. Also, results provided that the meropenem concentration required to reduce the GST activity to half equal to 1.266 mM. After applying the Line weaver-Burk blot and equation, it was noted that both Km and Vmax values decreased in the presence of meropenem, indicating uncompetitive inhibition. In conclusion, meropenem antibiotic is a potential inhibitor for GST. Therefore, it will be crucial to consider the metabolic defense systems when selecting the dosages of this antibiotic to be utilized for the treatment of infections.

Keywords: Meropenem antibiotic; Glutathione -S-transferase; Enzyme Inhibition.

INTRODUCTION

Glutathione-S-transferases (GST) are primarily found in phase II metabolism and protect several organisms through cellular defense against xenobiotics. These enzymes catalyze the synthesis and metabolism of exogenous and endogenous electrophilic xenobiotics [1- 3]. In fact, GST enzymes are divided into three major families, which are cytosolic, mitochondrial, and microsomal GST [4]. The first family of GST represents ten percent of cytosolic proteins that catalyze the conjugation of toxic xenobiotics and oxidatively produced compounds to reduced glutathione. Consequently, GST enzymes facilitate the metabolism and elimination of these compounds, which results in protection against oxidants [5]. Although all eukaryotic species have multiple GST isoenzymes, their pattern of expression is specific for species, age, and organs [6]. Notably, mammals have GST in all tissues and organs and are found in different forms. As stated by previous studies, liver, testes, kidney, adrenal glands, and jejunum had the highest levels of GST, whereas the thyroid, muscle, and bladder had the lowest levels [7-8]. Despite the apparent ubiquitous expression of GST, different GST genes may exhibit markedly varied expression patterns in various tissues, resulting in a unique and complex GST profile for each organ [9]. The biotransformation capabilities of some tissues and the possible genotoxicity of some carcinogens on those tissues are further affected by the inter-individual variability in GST profiles. In cancer cells, this diversity is somewhat more pronounced [9]. In view of that, human GST protein family exhibited notable structural homology and some degree of functional overlap [10]. In particular, the cytosolic GST are structurally similar enzymes that perform a variety of functions, including detoxification of xenobiotics, elimination of oxidative stress products, and modulation of the signaling pathways that trigger apoptosis and cell growth. These wide-ranging functional properties lead to several possible therapeutic utilization for isoform-specific GST inhibitors. These inhibitors have potential applications in the modulation of drug resistance in tumor cells, sensitization to therapeutically-directed oxidative stress, stimulation of cell proliferation, and augmentation of antimalarial medications. As the structure and function of GST have become more known, this leads to the successful use of mechanism-based inhibitors and rational design strategies [11]. In this regard, the effect of several antibiotics on the activity of GST enzyme has been investigated and reported in the literature. Some of these antibiotics are potential inhibitors for GST, including; amoxicillin, vancomycin, ampicillin, gentamicin, cefazolin, cefuroxime and amikacin [12- 15]. As far as we know, no previous research has investigated the impact of meropenem antibiotic on GST. This carbapenem antibiotic is a member of the β-lactam class that is stable to nearly all β-lactamases and exhibits broad-spectrum efficacy against both Gram-positive and Gram-negative bacteria. Compared to other carbapenems, meropenem is relatively stable to dehydropeptidase I (DHP-I) hydrolysis [16]. Similar to the other carbapenems, meropenem inhibits bacterial growth by binding to penicillin binding protein (PBP), thus interferes with bacterial cell wall synthesis [17]. Owing to its antimicrobial activity, meropenem is prescribed to treat bacterial meningitis, complicated intra-abdominal infections, and skin diseases as it demonstrated rapid and effective penetration in a wide range of tissues [18]. The pharmacodynamic profile of meropenem showed the time-dependent bactericidal target of (~40%T >MIC) [18]. Moreover, animal studies indicated that meropenem is present in most organs, including kidney, blood, and urine, that have the highest distribution. About half of the plasma levels of the drug were found in the rectum, prostate, thyroid, trachea, lymph nodes,

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liver, lung, skin, uterus, and ovaries [19]. Throughout the 250-1,000 mg dosage range, meropenem exhibited linear pharmacokinetics, with an elimination half-life of 0.83-1.24 hours. In addition to that, pharmacokinetic research demonstrated that 65%-79% of the drug is excreted as meropenem, while 19%-27% is excreted as ring-open lactam, the only metabolite of meropenem that is microbiologically inactive [19]. Based on the literature search, the in vitro effect of meropenem antibiotic on GST kinetics was not previously studied. So, the impact of meropenem antibiotic on the activity and kinetics of hepatic GST was demonstrated in this study.

METHODS

Purification of Glutathione-S-Transferase

Glutathione-S-transferase enzyme solution was obtained from the Protein Purification Laboratory, Biology and Biotechnology Department, Faculty of Science, An-Najah National University. The sheep was the source of the fresh liver in this experiment, and it was directly obtained from a slaughterhouse in Nablus city. At which all animals were under the ethics of the Ministry of Agriculture. The enzyme solution was prepared as follows: fresh sheep liver was homogenized at 4 °C in a ratio of 1:3 (w/v) with 50 mM phosphate buffer containing 1 mM EDTA, pH 7. The homogenate was centrifuged at 10,000 ´g for 25 min (Sorval Lynx 600), and the pellet was discarded. Then the obtained supernatant was centrifuged (Sorval Lynx 600) at 50,000 ´g for 120 min. The obtained supernatant (sheep liver cytosol (SLC)) was filtered and stored at -20°C. The prepared SLC was purified in three steps, starting with ammonium sulfate precipitation. The ammonium sulfate concentration was increased from zero to 30% in 50 ml of SLC at 4 °C. Then the mixture was centrifuged (Sorval Lynx 600) for 20 min at 10,000 ´g. The pellet was discarded, and the ammonium sulfate concentration was increased from 30% to 70% in the supernatant and centrifuged (Sorval Lynx 600) for 20 min at 10,000. The supernatant was discarded, and the pellet was dissolved in 0.2 M phosphate buffer, pH 7. The obtained solution is called ammonium sulfate fraction (ASF). The second purification step is gel filtration; in this protocol, GST enzymes were purified using (Ultragel ACA 44 column, Sigma). The column was equilibrated with 0.2 M phosphate buffer, pH 7. The ammonium sulfate fraction was applied and washed with 0.2 M phosphate buffer, pH 7, until no proteins were eluted from the column. All fractions were determined for protein level using the Warburg and Christian method and GST activity was determined by the Habig et al method [20-21]. The fractions with GST were pooled and called the gel filtration fraction (GFF). The final purification step was affinity column chromatography; during this purification step, the gel filtration fraction was applied to the affinity column (GSH-agarose, Sigma). The column was equilibrated with 5 column volumes in 0.2 M phosphate buffer, pH 7. The sample was applied and washed with 0.2 M phosphate buffer, pH 7, until no proteins appeared in the effluent. After elution using (Tris-HCl buffer pH, 9.6 containing 0.2 M NaCl and 10 mM reduced glutathione (GSH)), all fractions were determined for GST activity according to the Habig et al method and protein levels were determined by the Warburg and Christian method [20-21]. The fractions with GST activity were pooled, dialyzed, concentrated by freeze-drying to a concentration equal to 200 µg/mL, and subsequently used for the activity and kinetic studies.

Determination of Meropenem Antibiotic Effect on Glutathione-S-Transferase Activity

Glutathione-S-transferase activity was carried out spectrophotometrically at room temperature using 1-chloro-2,4-dinitrobenzene (CDNB, Sigma) as a substrate [20]. The cuvettes contained 0.2 M phosphate buffer (pH = 7), 1.5 mM reduced glutathione (GSH, Sigma), 1.5 mM CDNB and 50 uL of diluted enzyme (1 µg/mL) kept on ice in a final volume of 1 mL. A change in absorbance at 340 nm was followed against a blank containing all reactants except CDNB. The GST activity was expressed as µmol conjugate formed/min/mL using a molar extinction coefficient of 9.6 mM-1.cm-1. The effect of the antibiotic (meropenem, Laboratorio) at different concentrations (10, 7.5, 5, 2.5, 1, 0.5, and 0.25 mM) was measured by adding 50 uL from each antibiotic concentration to the enzyme reaction mixture. Then the effect of each antibiotic concentration on the activity of GST was measured by a spectrophotometer at 340 nm and expressed as an inhibition percentage.

$$\text{Inhibition \%} = (\text{GST activity without treatment} - \text{GST activity under treatment of specific antibiotic concentration}) / \text{GST activity without treatment} \times 100\ \%.$$

All concentrations were analyzed in triplicate. The results were expressed as the mean ± standard deviation (SD). The concentration giving 50% inhibition (IC50) was calculated by non-linear regression with the use of Microsoft Excel. The dose-response curve was obtained by plotting the percentage inhibition versus concentration.

Determination of Meropenem Antibiotic Effect on Glutathione-S-Transferase Kinetic Parameters

The kinetic values of GST for GSH and CDNB were determined as follows: different concentrations of GSH (0.25, 0.5, 0.75, 1, 1.25, and 1.5 mM) or CDNB (0.3, 0.6, 0.9, 1.2, and 1.5 mM) were varied. While the concentration of the other substrate was fixed at 1.5 mM. Fifty uL of purified enzyme (1 ug/mL) was added to 850 uL of working reagent (GSH) and 50 uL of distilled water for control. Then the reaction was initiated by adding 50 uL of the starting reagent (CDNB). The degree of absorbance at 340 nm was recorded for one min. Km and Vmax were calculated using Line weaver-Burk (LB) plot and equation. The same procedure was used to determine the effect of meropenem antibiotic on GST Km and Vmax values, except that 50 uL of distilled water were replaced by 50 uL of (2, 1, and 0.5 mM) meropenem antibiotic.

RESULTS

Effect of Meropenem Antibiotic on Glutathione-S-Transferase Activity

The first part of this research was to find out the effect of the meropenem antibiotic on hepatic GST activity (Table 1). The obtained results revealed that meropenem antibiotic demonstrated an inhibitory effect on GST activity in the tested concentration range (0.25-10 mM).

Table (1): Effect of meropenem antibiotic on the activity of GST.

	Meropenem Studied Concentrations (mM)							
GST Activity	Control	10	7.5	5	2.5	1	0.5	0.25
	6.3±0.11	0	0	0	0	3.5±0.10	3.8±0.09	4.4±0.12

Moreover, meropenem was found to display an inhibitory effect on the activity of GST at low concentrations (0.25, 0.5 and 1 mM), which resulted in 30.5, 39.4 and 45.1% inhibition, respectively (Figure 1). Furthermore, the meropenem concentration required to reduce the GST activity to half (IC50) is 1.266 mM.

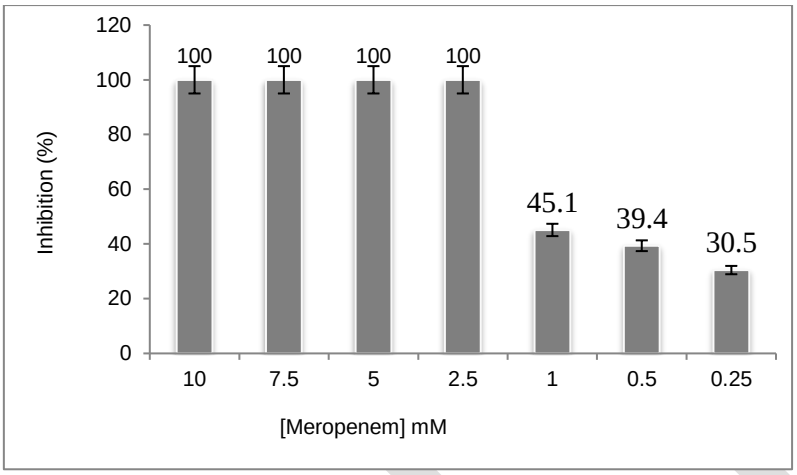
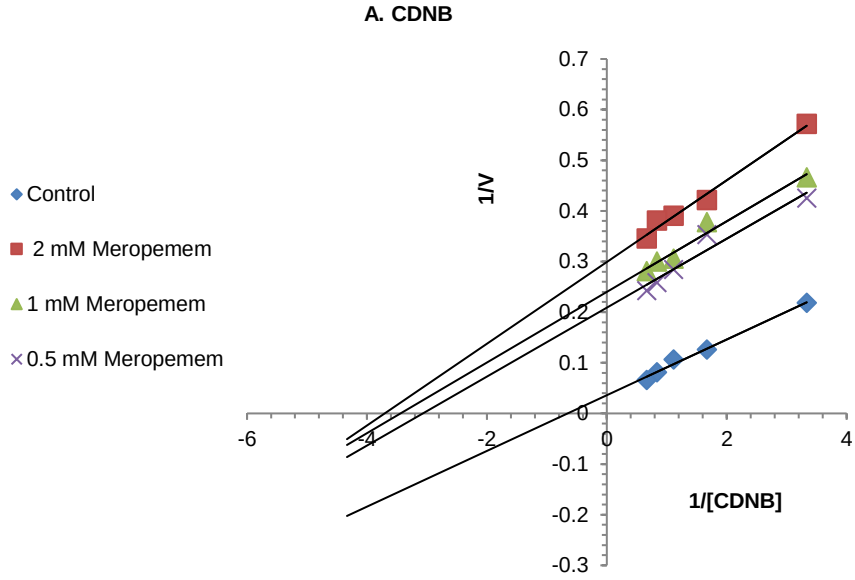


Figure (1): GST inhibition % at meropenem antibiotic different concentrations.

Effect of Meropenem Antibiotic on Glutathione-S-Transferase Kinetic Parameters

The kinetic parameters (Vmax and Km) were determined for GST with respect to CDNB and GSH at different concentrations in the absence and presence of meropenem at three concentrations (0.5, 1 and 2 mM) (Figure 2).



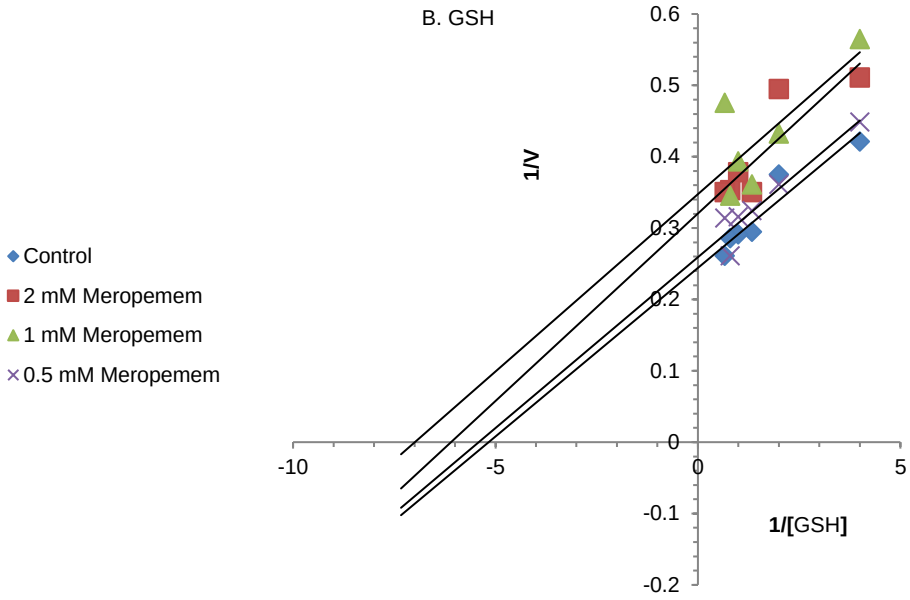


Figure (2): Lineweaver-Burk plots of GST at different A: CDNB and B: GSH concentrations and three different meropenem concentrations for determination of the kinetic parameters Vmax and Km and inhibition type.

After applying the LB blot and equation, it was noted that both Km and Vmax values calculated with respect to GSH and CDNB were decreased in the presence of meropenem (Table 2). These results indicate the uncompetitive inhibition effect of meropenem on GST.

Table (2): GST kinetic parameters Vmax and Km values with respect to CDNB and GSH as determined from the Lineweaver-Burk equation and plots.

Meropenem concentration (mM)	CDNB		GSH	
	Vmax (µmoles/min/mL)	Km (mM)	Vmax (µmoles/min/mL)	Km (mM)
0	28.571	1.571	4.098	0.205
0.5	4.808	0.327	3.861	0.193
1	4.167	0.287	3.125	0.156
2	3.344	0.268	2.881	0.144

DISCUSSION

Antibiotics are known to have negative effects on different organisms [22]. In recent years, the inhibition studies of many antibiotics have been performed extensively. These studies were conducted on various enzymes, including GST [14]. In addition to its antibacterial activity, meropenem could react with glutathione and nucleobases in DNA and could have an adverse effect on GST activity [17-18, 23]. Since there is no previous report concerning the effect of meropenem antibiotic on GST, this research was performed to figure out the effect of meropenem on the activity of GST. Inhibition studies in this investigation revealed that meropenem antibiotic inhibited GST enzyme at low concentrations and demonstrated that the tested meropenem is a strong inhibitor of GST. More specifically, the meropenem inhibitory percentage reached 100 % at a concentration of 2.5 mM or higher. Which in turn reflected the low concentration of this antibiotic (1.2662 mM) that is required to achieve 50 % inhibition of GST (IC50). So, further examinations were performed to emphasize the type of inhibition of meropenem antibiotic. In order to illustrate the type of inhibition of meropenem, the in vitro enzyme's kinetic studies were carried out by applying Lineweaver-Burk graphs and plotting. It is clearly noticed that meropenem is the medication that showed an uncompetitive inhibition type toward GST [24]. As, Km and Vmax values for GST with respect to GSH and CDNB decreased after the addition of meropenem at different concentrations. It is concluded that meropenem addition to GST decreases the maximum velocity of the enzyme and also decreases its affinity toward CDNB and GSH. Furthermore, this type of inhibition requires that one or more substrates bind to GST before the antibiotic can bind [24]. However, the binding of the inhibitor affects the binding of the substrate and vice versa [25-26]. Uncompetitive inhibitors could have dramatic physiological impacts. As the inhibitor decreases the enzyme activity, there is an increase in the local concentration of substrate. Without a mechanism to clear the buildup of substrate, the potency of the uncompetitive inhibitor will increase [27]. One possible explanation for the inhibitor's binding to the enzyme-substrate complex might be due to the enzyme's conformation changes after it binds to its substrate, forming or modifying a pocket that can be used for inhibitor interactions. In other cases, the substrate and inhibitor molecules may interact directly to enhance inhibitor binding [28]. This can be supported by molecular modeling analysis of morepenem. This analysis revealed that the molecular surfaces of meropenem abound to possess some electron-deficient regions so that these surfaces could react with glutathione, but the rate of this reaction may not be significant [23]. The previous findings proved that the binding of different chemicals, such as indocyanine green and 3,6-dibromosulfophtalein to GST is the major interaction mechanism of uncompetitive inhibitors [29]. This mechanism explains the inhibitory action of meropenem in the current experiment, as it may act as a non-substrate ligand that exhibits different inhibition kinetics. Moreover, scientists studied the effect of several compounds on the activity of GST. Few of the examined

compounds revealed uncompetitive inhibition, including hemin [30], indomethacin [31], dithiocarb [32-33], quinidine, quinine, tetracycline and pyrimethamine [34].

CONCLUSION

Meropenem antibiotic may be a potential inhibitor of GST isoenzymes. Due to the fact that GST plays a critical role in the host's defensive mechanisms against infection by up-regulating oxidative stress, it will be crucial to consider the metabolic defense systems when selecting the dosages of this antibiotic to be utilized for the treatment of infections. To achieve that, further in vivo experiments are required.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used and analyzed during this study are available from the corresponding author upon reasonable request.

Author's contribution: Lubna Abdallah: conceptualization, writing-original draft, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing review and editing. **Suha Daraghmeh:** writing-original draft, data curation, formal analysis, investigation, software, validation and visualization. **Toqa Bsharat;** writing-original draft, investigation, methodology, validation and visualization. **Najah Qraini;** writing-original draft, data curation, formal analysis, investigation, software, validation and visualization. **Suzan Kharraz;** writing-original draft, data curation, validation and visualization. **Nadeen Noor;** writing-original draft, data curation, validation and visualization. **Fatima Alhussni;** writing-original draft, data curation, formal analysis and visualization.

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Competing interest

The author declares that they have no competing interests.

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