INVESTIGATION OF THE EFFECTS OF SOME ANTICANCER AGENTS ON THE ACTIVITY OF MITOCHONDRIAL THIOREDOXIN REDUCTASE AND CYTOSOLIC GLUTATHIONE S-TRANSFERASE BY PURIFICATION, KINETIC AND MOLECULAR DOCKINGS STUDIES

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INTRODUCTION

While thioredoxin reductase (TrxR) plays an important role in the regulation of intracellular redox balance and various signalling pathways, glutathione S-transferase (GSTs) enzymes belong to detoxification family that catalyse the conjugation of glutathione with various endogenous and xenobiotic electrophiles. It is known that TrxR is overexpressed in many aggressive tumors and led to tumor growth and progression in cancer cells. GSTs detoxify xenobiotics from the cells thus provide resistance to chemotherapeutic anticancer drugs. Therefore, they have been identified as potential target to develop chemotherapeutic strategies.

METHODS

TrxR2 and GST were purified from rat liver having a specific activity of 0.436, 1640.930 EU/mg proteins with a yield of 39.2%, 31.280% and 207.6, 3516.584 of purification fold, respectively. After the purification procedure, in vitro inhibition effect of anticancer drugs (cisplatin, calcium folinate, carboplatin, epirubicin hydrochloride, doxorubicin hydrochloride, paclitaxel, etoposide, fluorouracil, and methotrexate) on both enzymes was investigated. Furthermore, molecular docking study was performed to determine the binding site and binding affinity of methotrexate to both rat TrxR2 and MGSTA1-1.

RESULTS AND DISCUSSION

TrxR2 was strongly inhibited by all of the anticancer drugs with the IC_{50} values of 0.29, 4.00, 4.70, 7.80, 8.30, 10.00, 48.00, 66.00, and 970 μM, respectively. GST was not inhibited by the anticancer drugs apart from methotrexate with 3.64 mM IC_{50} value. Finally, both enzymes were inhibited by only methotrexate in rat liver, and methotrexate was well placed in the active sites of both proteins. In terms of the data obtained from this study, methotrexate drug tends to develop less resistance during chemotherapy and it can be said that it is the best among the anticancer agents used in this study. Our findings are thought to be useful for the development of new chemotherapeutic strategies.