INTRODUCTION

Methotrexate is antifolate agent, used as one of the earliest cytotoxic drugs used in cancer therapy ***(Selqa, et al. 2008)***.

Methotrexate (MTX) is classified as an antimetabolic drug that is capable for blocking metabolism of the cells because it competitively inhibit dihydrofolate reductase (DHFR) enzyme. As a result of this effect, it has been found that MTX is helpful in treating certain diseases associated with abnormally rapid cell growth as cancer, psoriasis, rheumatoid arthritis and other autoimmune disease ***(Ciralik, et al. 2006)*.**

Cancer patients undergo variable side effects including vomiting, diarrhea and decrease nutrient absorption ***(Sukhotnik, et al. 2008)***.

These symptoms do not appear as direct action on gastrointestinal tract (GIT) but as consequences of inhibition of DHFR synthesis which affect not only tumor cells but also the rapidly dividing cells as crypts of mucosa of GIT, This is because DHFR is required to maintain the intracellular pool of tetrahydrofolate during purine and thymidine synthesis ***(Gao, et al. 2001b)*.**

So during treatment by MTX, there is damage and shortening of villi of small intestine ***(Johnston, et al. 2005)***.

It has been demonstrated that MTX treatment in rats induces several kinds of damage such as increased permeability, suppression of intestinal absorption of glucose and neutrophil infiltration in

intestinal lesions ***(Sukhotnik, et al. 2008).*** Recently, reactive oxygen species (ROS) production was detected in the small intestine of MTX treated rats ***(Gao, et al. 2002).*** So, oxidative stress plays an important role in the MTX-induced small intestine damage, especially neutrophil infiltration of oxidative stress would be useful in reducing intestinal damage in MTX treatment ***(Miyazono, et al. 2004).***

Vitamin A is essential for normal growth and differentiation of epithelial cells due to its anti-oxidant effect, so it has a protective effect from methotrexate-induced damage ***(Swartz-Brasile, et al. 2002)***.

Vitamin A coadminstration protects the salvage pathway of pyrimidine synthesis and the de novo purine synthesis in crypt cells ***(Kosakai, et al. 1991)***. Coadministration of vitamin A did not inhibit in_vivo antitumour activity of MTX ***(Naqai, et al. 1993).*** This protective effect of vitamin A may have clinical applications in cancer chemotherapy ***(Yuncu, et al.2004).***