Methotrexate (MTX), a folate antagonist, is an antineoplastic drug. MTX has side effects such as nephrotoxicity or hepatotoxicity. Evidence suggested that oxidative stress due to abnormal production of reactive oxygen species (ROS) has been accused in the etiology of MTX-induced nephrotoxicity and hepatotoxicity. In this study, we used PGE1 analogue misoprostol (MP) to reduce these damages. Rats were received a single injection of MTX (20 mg/kg, i.p.) with or without MP pretreatment (200 mcg/kg, orally). One half of kidney and liver tissues were investigated for histopathological examination by light microscopy. To biochemical examination, the other half of kidney and liver tissues were also obtained to determine lipid peroxidation product malondialdehyde (MDA) and activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT). MTX administration increased MDA production and decreased SOD and CAT levels in the kidney and liver tissues when compared to the control group. Morphological damage in MTX administrated rats were severe in the kidney and liver tissues. MP treatment caused positive effects on the above-mentioned parameters. These findings indicate that MP has beneficial effects on MTX induced nephrotoxicity and hepatotoxicity in rats.