Background Methotrexate (MTX) is an effective chemotherapeutic drug and is often accompanied by mucositis. Aim of the work To evaluate the efficacy of a-lipoic acid (LA) against the intestinal mucositis induced by MTX. Material and Methods fifty adult male albino rats were used in this study. The rats were divided into 5 groups (10 rats per each group). Control group : received saline i.p. injection. Short term MTX treated group: A single dose of MTX (20 mg/kg) was injected i.p. Short term MTX and LA treated group: A single dose of MTX (20 mg/kg) was injected i.p and LA (100 mg/kg) orally for 3 days. Long term MTX treated group: A single dose of MTX (0.75 mg/kg/week) was injected i.p for 3 weeks. Long term MTX and LA treated group: received a single dose of MTX (0.75 mg/kg) i.p and LA orally (50 mg/kg/day for 3 days) this was repeated for a total of 3 weeks. At the end of each period of the experiment, jejunal specimens were prepared for histological and ultrastructure examination. Results The methotrexate treated groups revealed different changes in the jejunum of rats. Distortion of the villi and crypts, epithelial atrophy inflammatory infiltration and goblet cell depletion were found. The use of electron microscope revealed ultrastructural changes in cell membrane, and cell organelles when compared with that of the control group. The MTX induced mucosal damage was improved with LA co-administration. Conclusion It can be concluded that the severity of jejunal damage caused by MTX treatment can be decreased with the concomitant use of LA. This protective effect of LA may have clinical applications in cancer chemotherapy.