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Beneficial effects of Chrysin against Methotrexate-induced hepatotoxicity via attenuation of oxidative stress and apoptosis

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Abstract Methotrexate (MTX), a folic acid antagonist, an effective chemotherapeutic agent is used in the treatment of a wide range of tumors and autoimmune diseases. Moreover, hepatotoxicity limits its clinical use. Several studies have already confirmed that the oxidative stress plays a major role in the pathogenesis of MTX-induced damage in the various organs especially in liver. The aim of this study was to determine the protective effect of Chrysin against MTX-induced hepatic oxidative stress and apoptosis in rats. In the present study, efficacy of Chrysin was investigated against hepatotoxicity caused by MTX in terms of biochemical investigations of antioxidant enzymes, apoptosis, and histopathological alteration in rat liver. In the MTX-treated group there was a significant increase in alanine transaminase, aspartate aminotransferase, lactate dehydrogenase activity and malondialdehyde content as well as decreased glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase activities and reduced glutathione content were also observed compared to the control group as a marker of oxidative stress. Histopathological alterations and apoptosis through the immunopositive staining of p53, cleaved caspases-3 and Bcl-2-associated X protein in rat liver were observed. Pretreatment of Chrysin at both doses prevents the hepatotoxicity by ameliorating oxidative stress, histopathological alterations, and apoptosis and thus our results suggest that Chrysin has a protective effect against hepatotoxicity induced by MTX and it may, therefore, improve the therapeutic index of MTX if co-administration is done.

Keywords Methotrexate · Oxidative stress · Apoptosis · Hepatotoxicity · Chrysin

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Introduction

Methotrexate (MTX) is a folate antagonist competitively inhibits dihydrofolate reductase (DHFR) hence it interferes with the nucleic acid synthesis. MTX is used for the treatment of different types of cancer, psoriasis, autoimmune disorders, and medical termination of pregnancy [1]. It has been well documented that hepatotoxicity is the major and potential side effect of MTX [2] which limits its clinical use. Although the exact mechanism of MTX-induced hepatotoxicity is not well known, several hypothesis have been given among which oxidative stress is well documented [3, 4]. MTX diminishes the antioxidant defense of the cell causing cells to become sensitized toward reactive oxygen species (ROS) [5]; ROS plays major role in promoting cell toward apoptosis [6]. MTX is used in chemotherapy regimen in which it does not discriminate between normal and malignant cells and hence promotes even normal cells toward apoptosis [7]. Many studies have been carried out to overcome the side effect of anticancer drugs by using natural product in its crude or purified form [8–10]. Flavonoids are naturally occurring compounds present in different plants in the form of fruits and vegetables [11]. Flavonoids can effectively decrease the risk of a number of diseases like cancer [12] and reported to be effective in case of diabetes [13], cardiovascular [14] and neurodegenerative diseases [15].