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Formononetin and biochanin A protects against ritonavir induced hepatotoxicity *via* modulation of NfκB/pAkt signaling molecules

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ABSTRACT

Aims: Ritonavir (RIT) is a human immune deficiency virus (HIV) protease inhibitor (PI) active against HIV-1 and HIV-2. Among various adverse effects of PIs, hepatotoxicity is a very common adverse reaction of RIT which is concentration dependent. Red clover isoflavones are found to possess anti-inflammatory, antioxidant and anti-apoptosis activity. Furthermore, recent studies have demonstrated that these isoflavones can be used to alleviate the side-effects of drugs. Hence, the present study was inquested to ascertain the effect of Formononetin (FMN) and Biochanin A (BCA) on RIT induced hepatotoxicity.

Main methods: Five groups of animals were subjected to treatment as control, toxic control (RIT), third group (RIT + FMN), fourth group (RIT + BCA), the fifth group (RIT + FMN + BCA) and sixth group (FMN + BCA) for 14 days. The animals were evaluated for estimation of liver toxicity markers, inflammatory biomarkers, *in-vivo* biochemical antioxidant parameters. The liver tissues were further evaluated histopathologically and western blotting examination for localization of apoptotic gene expression that plays a pivotal role in hepatotoxicity.

Key findings: FMN and BCA ameliorated the increased levels of biochemical markers of liver, attenuated the RIT induced Bax, caspase-3, NFκB and eNOS activation and persuaded the Bcl_2 and pAkt level. Alteration in the levels of inflammatory markers was also observed in both hepatic tissue and serum.

Significance: FMN and BCA exerts hepatoprotective effect through modulating the oxidative stress, inflammation, apoptosis and reversing the tissue degeneration suggesting its therapeutic role in hepatotoxicity and other hepatocellular diseases.

1. Introduction

An organ toxicity that remains of critical interest to drug development is that of hepatotoxicity [1,2]. Hepatotoxicity refers to liver dysfunction that is associated with an exposure to drugs or xenobiotics or any other non-infectious agents. Since, the liver is the main metabolic organ in the body and is exposed to the highest concentrations of orally consumed drugs, it is often considered as the target organ with ensuing drug-induced liver injury [3]. Certain medicinal and chemical agents when administered in overdoses or even at therapeutic dose or used in laboratories can damage the liver [5]. Many drugs have been reported to be hepatotoxic, which is the main cause for the withdrawal of the drugs from the market.

One of the most common marketed drugs that cause hepatotoxicity is the antiretrovirals. Since the introduction of antiretrovirals, protease inhibitors (PI's) are considered to be the requisite for the treatment of patients infected with Human Immunodeficiency Virus (HIV) as it is demarcated in sundry of national and international guidelines. Moreover, the prescribing information of the USFDA approved PIs includes the warning of hepatitis, hepatic failure or even death of the patient.

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