Abstract

Flavonoids are polyphenolic compounds present in our daily dietary sources. Apigenin, Genistein and Quercetin belong to this group and have been used as dietary supplement worldwide. Indiscriminate use of flavonoids by humans warrants dose-specific toxicity studies. In the present study, Apigenin, Genistein and Quercetin were selected and evaluated for their toxic effects on liver and kidney of Swiss mice due to their established pharmacological effect in humans. Mice were dosed with varying concentration of flavonoids to observe the toxic effects on the level of biomarkers of hepatotoxicity. Similar doses of flavonoids were used to study their effects on kidney. Lower doses of Apigenin (25 and 50 mg/kg), Genistein (125 and 250 mg/kg) and Quercetin (500 and 1000 mg/kg) did not cause any toxicity neither in liver nor in kidney. However, in higher flavonoids dosed groups (100 and 200 mg/kg Apigenin; 500 and 1000 mg/kg Genistein; 1500 and 2000 mg/kg Quercetin), increased biomarkers levels in serum of liver tissues were observed along with damaged histology of liver. Higher doses also cause the generation of ROS as indicated by its increase in PBMCs of higher treatment groups of Apigenin. LPO was raised and total Glutathione content was diminished in higher treatment groups of flavonoids. Protein content of SOD was decreased in the liver of higher treatment groups of Apigenin and Genistein. In contrast, it was increased in higher treatment groups of Quercetin. Alteration in the activities and mRNA level of other major antioxidant enzymes i.e. CAT, GPX, GR and GST were observed in the liver and kidneys of higher treatment groups of flavonoids. Expression of Hsp70 was found to decrease in higher treatment group of flavonoids. Gene expression analysis revealed a significant differential regulation of 48 genes consisting 36 up regulated and 12 down regulated. Most of them were engaged in regulation of apoptosis, oxidative stress and cell growth. Following Genistein exposure 40 differentially expressed genes were identified consisting of 20 up-regulated and 20 down-regulated and Quercetin exposure were identified 155 differentially expressed genes consisting 36 up-regulated and 119 down-regulated genes when p< 0.05 and 2 fold change criteria were applied. This study is the first comprehensive study at biochemical, histological and genomic level collectively to assess the flavonoids toxicity and their gene expression signatures. Differences in the chemical structure of flavonoids might be responsible for alteration at biochemical or genomic level. (Fig.1)
Figure 1: Diagrammatic representation of the overview of present study.