Abstract

Liver plays a vital role in almost all physiological processes and, injury to liver can affect health. There are various endogenous and exogenous agents present in the environment which directly or indirectly affect the function of liver like drugs, alcohols, xenobiotic compounds etc. Liver cells have ability to repair the damage because of its ability to regenerate new cells and it has various system reduces the toxic effects of chemicals. Due to continuous exposure of these agents, leads to cease the ability of cell to repair and produces ROS in the cells which again cause damage to cells. Liver cirrhosis is the final stage in which it cannot be cured but can be treated. But in the early stage of disease treatment can be possible.

Various allopathy medicines are available in the market and are most expensive and have various side effects. Developing a drug from medicinal plants or the use of plant’s part is cost-effective and have less or no side effects. So, in the current study, we evaluate and compare the antioxidant, anti-inflammatory and hepatoprotective activities of selected Ficus species of Karnataka namely F. parasitica, F. tsiela, F. microcarpa, F. heterophylla, F. dalhousiae, F. drupacea and F. mollis. Bark and leaf samples were used for the present studies extracted with different solvent hexane, ethyl acetate and methanol. Total phenolic content of selected Ficus species were determined which suggested that F. dalhousiae bark methanolic (FdBM) extract contained high amount of total phenolics compared to all other plant samples.

Later the selected bark and leaf samples were evaluated for in vitro antioxidant activity by using DPPH, ABTS, hydroxyl radical and nitric oxide radical scavenging and anti-inflammatory activities by using LOX and COX-2 inhibitory assay and IC_{50} values were calculated and methanolic extracts of F. dalhousiae and F. tsiela exhibited significant activity and have very less IC_{50} values. These two plants were selected for in vivo hepatoprotective activity in
CCl₄-induced hepatotoxicity in rats and both bark and leaf samples were used. Hepatoprotective activity were evaluated by using following parameters serum biomarkers, determination of liver antioxidants, ROS contents and histopathological studies. All samples possessed hepatoprotective activity but F. dalhousiae bark methanolic (FdBM) extract were best among all the samples. FdBM extract significantly decreased the level of serum biomarkers like AST, ALT, ALP and LDH, elevated the intracellular concentration of antioxidant enzyme, SOD, CAT and GSH and reduced the activity of ROS. Therefore, FdBM extract was selected for the isolation, characterization and identification of bioactive molecules.

The bioactive molecule isolated was naringenin which belongs to flavonoid group and has very good bioactivity. Again naringenin was used for in vivo hepatoprotective studies in paracetamol-induced hepatotoxicity on rats. Naringenin inhibited the activity of serum biomarkers. The depleted level of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione content in paracetamol-induced hepatotoxicity on rats was prevented by naringenin. Furthermore, naringenin inhibited oxidative stress by inhibiting lipid peroxidation process and ROS level in the tissue samples. In addition to this enzyme –linked immunosorbent assay for TNF-α and IL-6 revealed that naringenin downregulated the expression of this cytokines, because cytokines activates HSCs which further activates various other cytokines and finally it damages hepatic cells. So, inhibition of these cytokines revealed the protection of hepatic cells from injuries. In silico studies also revealed the protective role of naringenin as the molecular docking studies suggested that naringenin inhibits the expression of MMP-2, H-RAS GTPase, Human Arginase-2, PROMMP-2/TIMP-2 complex and NF-kappaB, which are responsible for the activation of hepatic stellate cells (HSCs) that stimuli the expression of other cytokines and lead to liver damages. Molecular docking also revealed that the binding of naringenin with IL-10 and IL-13 was very weak and have very low XP GScore, it
showed that naringenin doesn’t affect the expression of cytokines which helps in repair mechanism of liver during liver disease as compared with positive control silibilin.

Thus the present study suggests that the naringenin is the compound isolated from *F. dalhousiae* bark methanolic (FdBM) extract which was responsible for its bioactivity and it worth to consider as potent molecule against hepatic damage or liver diseases. Further, naringenin could be a novel tool for discovery and development of its analogue against liver disease.