Several studies have shown that liver is a susceptible organ and is injured by the administered drugs, most common of which includes the Non-steroidal anti-inflammatory drugs such as Paracetamol, Ibuprofen, Diclofenac, Sulindac; antitubercular drugs like Isoniazid, Rifampicin. However, the discovery of NSAID-induced hepatic damage first occurred in 1946, yet they were commonly used preparations during 60’s, which continued even in the current era, as Non Steroidal Anti Inflammatory Drugs are one of the commonly used over-the-counter (OTC) preparations [95].

Of all the Non Steroidal Anti Inflammatory Drugs, Diclofenac is most widely used in the world [140,141]. However, there were no more than 60 cases of diclofenac-induced hepatotoxicity that were reported until Banks and coworkers reported in 1995 [142]. Hence, we considered Diclofenac for evaluation of its hepatotoxic effects at various doses, considering the oral LD50 in albino rats.

It has been proposed that supplementation of DL-Methionine can ameliorate the liver injury and reduce the development of hepatic cell carcinoma in chronic liver disease, by abolishing the oxidative stress and the cellular damage that would be caused by the hepatotoxic drugs [143]. This is being achieved by the generation of antioxidant enzymes such as Superoxide Dismutase (SOD), glutathione peroxidase and catalase, along with the ability to scavenge the free radicals [144]. Further, inhibition of apoptosis, and reduction of cholestasis may further contribute to the hepatoprotective effect of DL-Methionine.
N-Acetylcysteine has been the drug of choice for the treatment of Paracetamol poisoning. It is rapidly known to hydrolyse to cysteine as compared to Methionine; hence it is quicker in its onset of action than compared to Methionine. Its efficacy in the treatment in Paracetamol-overdose has been evident in a recent Cochrane based meta-analytical study by Brok et al, 2006. World Health Organization on analyzing the randomized trials found that N-acetylcysteine is comparably effective in its hepatoprotective action when compared with DL-Methionine. This observation of Brok et al, was similar to that of Prescott, 1979; who proved N-Acetylcysteine to be a better hepatoprotective agent, since it dramatically reduced the severe liver damage induced by Paracetamol. Although both, N-Acetylcysteine and DL-Methionine facilitated de novo glutathione synthesis, N-Acetylcysteine showed a faster replenishment of the glutathione stores than methionine.

In the present study, Diclofenac Sodium in the doses of 72, 96 and 240 mg/kg, showed increase in the serum transaminases levels, indicating the liver injury caused by the drug. This observation of ours concurs with the results of Basavraj et al, (2012); in which it shows that the serum transaminase enzymes were elevated indicating the hepatotoxicity induced by Diclofenac sodium. It was also observed that our findings pertaining to the hepatotoxicity induced by diclofenac sodium, resembled with those observations made by Zeynab et al, 2013; to show that there was a significant rise in serum SGPT and SGOT levels in the rats following administration of Diclofenac sodium, which indicated hepatotoxicity.

DL-Methionine unlike N-Acetylcysteine has also been used in the treatment of Paracetamol poisoning and it has been demonstrated to be comparatively effective in
decreasing the hepatotoxicity induced by Paracetamol although, N-acetylcysteine is considered to be superior over DL-Methionine \cite{145}.

Since it was shown that oral DL-Methionine was highly effective in preventing the hepatotoxicity, in the present study, we first evaluated for it’s per se effect on the liver, which showed no significant changes in the biochemical parameters as well as the histopathological findings.

However, with the prior administration of DL-Methionine, followed by Diclofenac Sodium in the dose of 96 and 240 mg/kg, we could demonstrate the hepatoprotective effect of DL-Methionine on the hepatotoxic effect of Diclofenac Sodium, which was evident with the significant reduction in the biochemical parameters both SGPT and SGOT levels. Similarly, the hepatoprotective effect of DL-Methionine was evident with the histopathological findings which revealed the normal parenchymal cells and restoration of portal area to normal.

This observation of ours, resembles with those demonstrated by Rajesh Thatavarthi et al, (2011) \cite{151}, in which the authors have demonstrated the role of racemethionine hepatoprotective effect on the antitubercular drugs rifampicin-induced hepatotoxicity in albino rats, where they found that the racemethionine treated animals significantly showed a decrease in the biochemical parameters such as serum SGPT and SGOT and alkaline phosphatase levels indicating the hepatoprotective effect of racemethionine. It was also observed that these authors in their study concluded racemethionine as an antidote for Paracetamol overdose indicating it to be a more hepatoprotective drug against rifampicin –induced hepatotoxicity in experimental animals.

Similarly, Dass E, Shah KK \cite{132}, in their study have shown that DL-Methionine is more hepatoprotective than N-Acetylcysteine for Paracetamol induced toxicity. The authors
however, have proved the hepatoprotective effect of DL-Methionine against Chloroquine and Paracetamol-induced hepatotoxicity, which resembles with the observations made by us in the present study.

In our present study, we have observed that, in the presence of N-Acetylcysteine per se there occurred no changes in the level of serum enzymes. However, with the prior administration of N-Acetylcysteine followed by Diclofenac Sodium in the dose of 96 and 240 mg/kg, we could demonstrate the hepatoprotective effect of N-Acetylcysteine on hepatotoxic drug which was evident in the significant reduction in the serum SGPT and SGOT levels.

The histopathological examination showed the gross appearance of the liver to be similar to that of the control treated rats, with no change in the texture, while the microscopic examination showed that the hepatotoxic changes caused by Diclofenac Sodium in the form of diffuse hepatic vacuolation was abolished and the liver tissue showed normal parenchymal cells, with recovered portal area. These histological observations indicated that N-Acetylcysteine had hepatoprotective effect against the hepatotoxicity induced by diclofenac sodium. This observation of ours, concur with those of Veena Naik et al, (2011)\cite{133}, who showed that N-Acetylcysteine had reduced the serum enzymes like SGOT, SGPT and alkaline phosphatase levels and also have proven the hepatoprotective effect of N-Acetylcysteine with their histopathological findings.

Similarly, Librado A, et al, 2015\cite{152}, have proved that N-Acetylcysteine is effective in its hepatoprotective action, while they have compared its activity with Ficus Pseudopalma Blanco against Paracetamol-induced liver toxicity in rats\cite{152}. Furthermore, our observations concur with those of Claudia Zwingmann and Marc B,
(2006)\textsuperscript{153}, to show that \textit{N}-Acetylcysteine is effective as hepatoprotective agent against NSAID-induced toxicity. It reduces the levels of serum enzymes and the apoptosis, thus protecting the hepatic tissue against the damage caused by the hepatotoxic drugs.

Similarly, the observations of Basavraj S et al, (2012)\textsuperscript{149}, resembles the findings to that found in our studies, which show that \textit{N}-Acetylcysteine has hepatoprotective effect by reducing the raised serum enzyme levels caused by Diclofenac-induced toxicity.

Further, we have compared for the effectiveness of \textit{DL}-Methionine and \textit{N}-Acetylcysteine for their hepatoprotective effect against Diclofenac-induced hepatotoxicity, where we have observed, both \textit{DL}-Methionine and \textit{N}-Acetylcysteine reduces the serum transaminases levels, that were elevated due to the hepatotoxic effect of diclofenac sodium and these observations were further proved by the histopathological findings as well.

Further, we have observed that both \textit{DL}-Methionine and \textit{N}-Acetylcysteine were effective as hepatoprotective agents against Diclofenac-induced hepatotoxicity.