Out of the forty polyherbal formulations available in India for liver disorders eighteen have been tested for antihepatotoxic activity in rats intoxicated with CCl$_4$. Three of these formulations viz., Kalmegh Compound, Livergen and Stimuliv, were found to be highly effective in inhibiting CCl$_4$-induced increase in the levels of serum transaminases.

Based on the frequency of use in the commercial formulations, four plants - *Andrographis paniculata*, *Eclipta alba*, *Plumbago zeylanica* and *Tephrosia purpurea*, were selected for the present investigations. Petroleum ether, chloroform, methanol, aqueous and total aqueous extracts of each of the plant under investigation were screened for antihepatotoxic activity in CCl$_4$ intoxicated rats. The methanolic extract of *A. paniculata* exhibiting 62% overall reduction in CCl$_4$-induced increase in the levels of serum transaminases, serum alkaline phosphatase and serum bilirubin was found to be the most active of all the extracts tested and was, therefore, selected for detailed antihepatotoxic investigations.

In order to ascertain if the activity of the methanolic extract of *A. paniculata* was due to andrographolide - the major diterpenoid lactone present in the extract, or due to other constituents of the extracts, andrographolide was isolated from the extract and its identity confirmed by co-TLC and by comparing its m.p., UV and IR spectra with the reference andrographolide. Its hepatoprotective activity was compared with that of the methanolic extract (containing equivalent amount of andrographolide) and the andrographolide-free-methanolic extract (in a dose comparable to that of the
methanolic extract) using CCl₄ intoxicated rats. Andrographolide was found to exhibit maximum protective effect as indicated by biochemical and histopathological observations. Andrographolide-free-methanolic extract has been found to be least active indicating andrographolide to be the major antihepatotoxic principle of A. paniculata.

Quantitative estimation of andrographolide has been done by HPLC, and this method was found to be 3000 times more sensitive than the already known TLC-UV method. Highest concentration of andrographolide was found in the leaves (2.39%) followed by the root (0.44%), the stem (0.20%), the pericarp (0.18%) and the seed (0.13%) of A. paniculata. The active methanolic extract of the plant was found to contain 11.61% of andrographolide.

Acute toxicity studies with andrographolide revealed its LD₅₀ as 11.46g/kg, i.p., in male mice. Administration of andrographolide to mice for four days at 100mg/kg, i.p., or to rats at 50mg/kg, p.o., dose level for fourteen days did not alter liver function as confirmed by biochemical and histopathological observations indicating andrographolide to be safe as far as its effect on liver function is concerned.

Antihapatotoxic activity of andrographolide has been evaluated using CCl₄, GaIN, PcmL and EtOH models of liver toxicity. Apart from the inhibition of hepatotoxin induced increase in the levels of various biochemical parameters, and significant improvement in histopathological profile in rats, andrographolide also significantly normalised CCl₄-induced increase in the
pentobarbitone induced sleep time. Treatment of rats with intraperitoneally or orally administered andrographolide prior to GalN challenge showed a dose dependent hepatoprotective effect. Pre- and post-treatment of rats at different time intervals with andrographolide exhibited that maximum inhibition of GalN-induced biochemical changes occurred when andrographolide was administered prior to GalN challenge. In PcmL model, half the dose of andrographolide was found to be as effective as that required in case of the GalN model. Further, in case of PcmL hepatotoxicity, post-treatment of rats with andrographolide was observed to be more effective than the pretreatment unlike GalN hepatotoxicity. In EtOH model, treatment of rats concurrently with EtOH and andrographolide significantly normalised EtOH-induced biochemical and histopathological changes in the liver.

Andrographolide has been found to have antihepatotoxic activity comparable to silymarin, the well established hepatoprotective natural product, against CCl₄, GalN and PcmL intoxication in rats.

As all the four hepatotoxins used for evaluating hepatoprotective activity of andrographolide differ in the induction mechanism of liver injury, it is quite likely that andrographolide exerts hepatoprotective action by a variety of modes of action such as alteration or stabilization of plasma membranes, inhibition of microsomal enzymes or lipid peroxidation, stimulation of hepatic regeneration or by modifying the immune response.