Chapter-VII

Conclusion
Etoposide therapeutics is seriously affected by various undesirable properties such as poor solubility, narrow therapeutic index and efflux transporter specificity. Oral bioavailability of etoposide is poor and highly variable, mainly due to: (1) cytochrome P450 (CYP) activity and (2) drug transporters, in gut wall and liver. Among various efflux transporters, P-glycoprotein (P-gp) has received enormous attention in both cancer research and pharmaceutical field. P-gp transporter impedes the permeability of drugs through physiological barriers producing limited pharmacological response. It influences absorption, by expelling drug molecules back into the gastrointestinal (GI) lumen; distribution, by preventing entry into tissues like brain; metabolism, as it acts synergistically with CYP 3A4; excretion, by affecting both biliary and renal tubular function. Apart from P-gp other drug-transporting systems and CYP effects also determine overall oral drug uptake [203].

These biochemical barriers responsible for the poor/variable bioavailability may be overcome by co-administration of agents, able to inhibit P-gp /CYP enzymes that allow the drug to bypass efflux pump transport/ pre-systemic metabolism.

In recent times this approach is widely explored thus opening new vistas in oral chemotherapeutics. In the present investigation we have focused on the characterization of a novel piperine analogue PA-1 that may play a significant role in regulation of oral bioavailability of etoposide.

The major findings of the present investigation have revealed that:

- PA-1 modifies the pharmacokinetics of etoposide in mice as reflected in higher $C_{max}$, and AUC, decreased clearance and longer half-life of co-dosed etoposide.
PA-1 enhances the absolute bioavailability of co-dosed etoposide in mice by 2.3 fold.

PA-1 is a dual inhibitor of P-gp /CYP 3A4.

PA-1 enhances etoposide absorption and prevents its efflux across GIT.

PA-1 thus co-dosed with etoposide enhances oral bioavailability of etoposide by decreasing its systemic clearance via increasing its (i) intestinal absorption, and (ii) by inhibiting P-gp/CYP 3A4 disposition mechanisms thus preventing its efflux and inactivation during its transit from intestine to the systemic circulation.

The vast majority of interactions which are characterized by a decrease in systemic drug clearance may result in a need to reduce the dose of anticancer drug. There exists a possibility of identifying a low dose combination of etoposide with PA-1, having bioequivalent therapeutic effect with reduced toxicity implications in comparison to standard regimen of etoposide.