CHAPTER-2

LITERATURE SURVEY

1. **Vijay Saradhi Mettu et al., (2015)** performed *in-vivo and in-vitro* pharmacokinetics studies of Ritonavir and Ketoconozole, altered the Repaglinide pharmacokinetics. In both the studies, the drug-drug interactions were found to be very strong and the dose of Repaglinide was decreased to 20 folds [46].

2. **Jin-Seok Choi et al., (2013)** investigated effect of Nifedipine on P-gp and CYP3A4 activity. The blood glucose concentrations and pharmacokinetic parameters of Repaglinide in rats after oral and i.v administration of Repaglinide to the rats in the absence and presence of Nifedipine increased bioavailability of Repaglinide which was due to inhibition of CYP3A4 mediated metabolism of Repaglinide in the liver and /or small intestine [47].

3. **Chong–Ki Lee et al., (2013)** studied the blood glucose concentrations and the pharmacokinetic parameters which were determined in the absence and presence of Fluvastatin. In this study the authors concluded that close monitoring is essential for concurrent use of Repaglinide due to potential drug interaction [48].

4. **Sekhar Makula et al., (2012)** studied the influence of Atorvastatin on the pharmacodynamic and pharmacokinetic activity of Repaglinide in rats and rabbits. At different time intervals, the blood glucose levels and Repaglinide plasma concentrations were estimated. The enhanced glucose metabolism of Atorvastatin played a significant role and the levels of Repaglinide were increased by competitive CYP3A4 enzyme inhibition by Atorvastatin [49].

5. **Makula Chandra Sekhar et al., (2012)** studied Simvastatin/ Repaglinide/ Simvastatin+Repaglinide which were administrated to the normal rats, diabetic rats and to normal rabbits orally. In this study the authors concluded
that in animal models, co-administration of Simvastatin was not improved Repaglinide responses significantly [50].

6. Carolina Sall et al., (2012) conducted a study in which the main aim of the study was to perform a comprehensive investigation of Repaglinide metabolic pathways and assess their contribution to the overall clearance. Between CYP3A4 and CYP2C8 for M1 and M4 formation, distinct differences in clearance ratios were observed. For the assessment of drug-drug interactions the Repaglinide M4 metabolic pathway was proposed as a specific CYP2C8 probe [51].

7. Dong-Hyun Choi et al., (2011) concluded that the increased bioavailability of Repaglinide could be attributable to the inhibition of the CYP3A4 medicated metabolism in the small intestine and/or in the liver rather than both to inhibition of P-gp in the small intestine and to reduction of renal elimination of Repaglinide by Amlodipine. When co-administering Repaglinide and Amlodipine, the enhanced oral bioavailability of Repaglinide should be taken into consideration due to potential drug-drug interactions [52].

8. Madhukar. A et al., (2011) investigated; a single dose of Losartan (10mg/kg) was treated with Efavirenz (100mg/kg) and Ritonavir (10mg/kg) daily. The bioavailability of Losartan was decreased with co-administration of Ritonavir in low amounts on day 1 and increased the bioavailability of Losartan due to repeated dose administration which increased the antihypertensive activity [53].

9. SK. Mastan et al., (2010) investigated and concluded that at metabolic level, the interaction between Atazanavir and Gliclazide was observed to be pharmacokinetic interaction in animal models [54].

10. SK. Mastan et al., (2009) described the possible metabolic interaction between antiretroviral drugs and oral hypoglycemic drugs. All HIV PIs and
NNRTIs were metabolized by CYP3A4 isoform and each of these drugs may modify the metabolism of the co-administered drugs including other antiretroviral drugs. CYP2C9 metabolizes sulphonylureas and CYP3A4 metabolizes Gliclazide, Pioglitazone, Nateglinide and Troglitazone. In this review, the authors recommended that well designed drug-drug interaction studies are very much essential to determine whether antiretroviral drugs can be safely co-administered with the drugs that can be used to treat the diabetic complications with HIV infection [55].

11. S.K. Mastan et al., (2009), examined and reported significant hyperglycemia was produced by Indinavir at 1h in rats (normal and diabetic) and rabbits. They concluded that dose adjustment might be needed for the combination and at the time of prescribing care should be taken for clinical benefits in patients with diabetes [56].

12. Elke S. Perloff et al., (2005) evaluated and concluded that Atazanavir is a CYP3A potent inhibitor and an inhibitor and inducer of P-gp in-vitro that suggested Atazanavir to cause drug-drug interactions in-vivo [57].

13. Lauri I. Kajosaari et al., (2004) conducted randomized, three phase cross-over study in which Bezaibrate at a dose of 400mg, Fenofibrate at a dose of 200mg or placebo were received by 12 healthy subjects OD for 5 days. Repaglinide was administrated at a dose of 0.25mg and 1hour after the last pretreatment dose on fifth day. Up to 7 hour post dose, the plasma concentration of Repaglinide, Bezaibrate and Fenofibrate and blood glucose were estimated. Finally the authors concluded that the pharmacodynamics or pharmacokinetics of Repaglinide was not affected by Bezaibrate and Fenofibrate [58].

14. Tanja Busk Bidstrup et al., (2003) noticed that both CYP3A4 and CYP2C8 had a significant role in the human in-vitro biotransformation of Repaglinide was confirmed by the results. A better understanding of the variations in AUC
and $C_{\text{max}}$ observed within patient groups treated with Repaglinide was lead by the differences in the activities of these enzymes and also explained the reason for selective inhibition and possibly induction of CYP3A4 in humans has a less than expected effect on Repaglinide pharmacokinetic [59].

15. Jon F. Denissen et al., (1996) investigated the metabolism and disposition of $[^{14}\text{C}]$ – Ritonavir. In all the three species, Ritonavir was cleared primarily via hepatobiliary elimination. Extensive metabolism of Ritonavir was indicated by all the three species and was analyzed by Radio-HPLC. In dog glucuronide metabolites were observed. In all the species, plasma protein binding of Ritonavir was high and in humans it was nonsaturable at concentrations up to 30µg/ml. [60].