7. Summary

Studies to assess the extent of herb-drug interaction are essential in India, where the population is exposed to multiple systems of medicine. In conditions like type-2 diabetes, patients tend to add herbal medicines with or without physician’s knowledge to the anti-diabetic medication. Label of prescribed drugs does not give information on herb-drug interaction details as extensively as drug-drug interactions and there is a lack of herb-drug interaction reporting, especially with the Indian herbal medicines. We investigated two herbal medicines, ashwagandha and sallaki, used extensively in India for various chronic ailments, for possible pharmacokinetic and pharmacodynamic interactions with most commonly prescribed anti-diabetic drugs, glibenclamide (a hypoglycemic agent) and metformin (an anti-hyperglycemic agent). The study involved development and validation of bioanalytical methods for the estimation of glibenclamide and metformin, development and optimization of insulin resistant rat model and PK-PD evaluation of glibenclamide and metformin in presence of selected herbs in normal and insulin resistant rodents.

Bioanalytical methods were developed and validated for glibenclamide and metformin with the linearity range of 10 to 1200 ng/mL and 60 to 9000 ng/mL for glibenclamide and metformin respectively. The developed methods were specific, precise and accurate over the specified linearity range. The stability studies showed that the drugs were stable in plasma at room temperature for seven hours, 30 hours at 4°C, 70 days at -20°C and after three freeze thaw cycles, making the methods suitable for planned pharmacokinetic interaction experiments.

Optimization experiment for insulin resistance rodent model was based on previously reported insulin resistance/NIDDM models like high fat diet model, high calorie diet model and high fat diet with low dose streptozotocin. We did not find encouraging results with combination of high carbohydrate diet and STZ. Significant number of HCD rats died post STZ injection (i.p.) presumably due to complications of severe hyperglycemia. We optimized high carbohydrate diet composition to 55% of sucrose, 28.1% normal pellet diet, 1.5% of fat and the remaining was made up with casein, cellulose, cholesterol, choline, vitamins and minerals. After continuously feeding the rats with this modified diet for six months, significant weight gain was observed. Additional supplementation of 30% sucrose solution in drinking water led to further aggravation of the condition resulting in prompt insulin resistance and impaired glucose tolerance. The histopathological examination revealed swollen adipose tissue and presence of fatty liver and associated pathological modifications.
aggravating insulin resistance. The liver enzymes and serum TG levels were abnormally high, simulating the condition of pre-diabetes in humans.

Pharmacokinetic and pharmacodynamic experiments were performed in both normal and insulin resistant rats. PK studies involved comparison of pharmacokinetic profile and parameters of anti-diabetic drugs (GLI or MET) in presence of selected herbs (ASH and SAL), either as simultaneous administration or as pretreatment with respective controls (drug alone). PD evaluation involved assessment of plasma glucose values obtained simultaneously with PK data and assessment of insulin levels at select time points (only in IR rats).

The PK-PD studies demonstrated potentiation of glibenclamide effect after pretreatment of ASH and SAL by enhancing the bioavailability of glibenclamide and possibly by exerting their own hypoglycemic property. This indicates a possibility for potential therapeutic strategy where adequate glycemic control may be achieved with much lower dose of GLI with ASH or SAL pretreatment. MET PK-PD study demonstrated that increased obesity and associated pathological changes led to increased systemic exposure of metformin. In the absence of herbs, MET glucose profile was stable with a narrow range of plasma glucose variations. ASH does not affect MET-PK. Administration of SAL reduces the bioavailability of metformin. In presence of ongoing SAL treatment, higher doses of MET may be required to produce required effect.