ABSTRACT

India is one of the 12 mega biodiversity zone covering 2.4% of world’s area but with 8% of global biodiversity. It includes 15 agro-climatic zones containing about 47,000 plant species including nearly 15,000 medicinal plants. More than 25000 single or polyherbal formulations are used by the tribal and rural population in India. Export – Imports bank reports reveals that, the global trade of plant derived and plant originated products of around US $62 billion (with growth of 7% per annum) where India holds stake US $1 billion. There is an urgent need to cherish these in both the National and International perspectives for the benefit of mankind. Apart from healthcare, medicinal plant trade is an important alternative income generating source for under-privileged communities. Thus, there is an urgent need of the scientific base evaluation of a herbal system of medicine for accepting international regulatory guideline to get drug approval status.

Taking these views into consideration, US patented polyherbal formulation consists of *Salacia oblonga*, *Salacia roxburghii*, *Garcinia indica* and *Lagestroemia parviflora* was developed for the prevention and management of Type II Diabetes and its vascular complications associated with diabetes mellitus (D-formulation) and European patent consists of leaves of *Bacopa monnieri* (Scrophulariaceae), fruits of *Hipphophae rhamnoides* (Elaganaceae) and bulbs of *Dioscorea bulbifera* (Dioscoraceae) (N-Formulation) was developed for the management of cardiovascular and neurological disorders were selected for the present research work to standardize, to investigate the pharmacokinetics and pharmacodynamics of the major bioactive compounds present in the formulations.
These capsules and individual plants extracts were subjected to preliminary phytochemical, physiochemical and quality control parameters according to WHO guidelines and Indian Pharmacopoeia. The results were indicating that, all the values are within the limits and can be preferred to consume by mankind for various medicinal purpose.

For the modernization of herbal medicine, study of the pharmacokinetics was an important aspect. Mangiferin was choosen as a target compound for the D formulation. A simple and sensitive LC-MS bioanalytical method was developed and validated for pharmacokinetic study of Mangiferin. Pharmacokinetic results showed that, Mangiferin was rapidly absorbed into the portal vein after oral administration of Mangiferin alone with greater rate of absorption constant and higher volume of distribution. When it was administered in the form of formulation, there will be an increase in AUC, which indicated that, higher amount of Mangiferin was absorbed from the formulation. The increased AUC of Mangiferin after administration of formulation might be due to the presence of, other biomarkers in the formulation which shows the greater binding effect to the human serum albumin.

Tissue distribution of the Mangiferin was investigated in rats following a single oral dose of polyherbal formulation (30mg/kg equivalent to Mangiferin). Mangiferin underwent a rapid and wide distribution into tissues within the time course examined. The highest concentration of Mangiferin was detected in the small intestine (754.2 ng/mL of homogenate). On the other hand, Mangiferin could hardly accumulate in the brain as the levels were well below the LOQ. Due to its hydrophilic character, it was difficult to pass the blood brain barrier (BBB). Mangiferin was effectively distributed
into the extravascular system of rat body with substantial disposition in kidney, liver, suggesting that renal and hepatic metabolisms were the primary elimination routes.

The relative bioavailability of Mangiferin from the patented polyherbal formulation was investigated. Although being fundamental research, the results of this study provide valuable information for the development and clinical utility of polyherbal formulations.

A systematic and comparative investigation of the metabolism and pharmacokinetics of mangiferin was studied in Wistar rats through intraperitoneal and oral route of administration by sensitive and specific LC-ESI-MS. The structures of the metabolites were unambiguously identified or tentatively proposed by comparing their fragmentation patterns with those of standards, basis of their precursor ions, product ions and HPLC retention time. The biotransformation pathway of Mangiferin in rats elucidated on the basis of that results help us to understand the effective dosage form to get high free drug concentration which will enhance the bioavailability and pharmacological effect.

An open label and single dose pharmacokinetic study of Mangiferin present in the polyherbal formulation was carried out in healthy, adult, male, human subjects under fasting conditions. It was found that, the pharmacokinetics of Mangiferin was highly variable in individuals. The values of the pharmacokinetics parameters $C_{\text{max}}$ was 95.13ng/mL reaches at time 3.50hrs. $AUC_{\text{inf}}$ was 494.06ng hr/mL while half-life was 3.60hrs. Clinical pharmacokinetic data of Mangiferin from the formulation was similar to the preclinical studies. Whereas the bioavailability of Mangiferin was very low from the formulation in human volunteers reaches its maximum plasma concentration about
95.13ng/mL at 3.50hrs of $T_{\text{max}}$. There is a rapid decline in plasma concentration after 4.00hrs and after 6 hours the plasma concentration was lower than LOQ.

Quercetin and Rutin flavonoid compounds were major constituents considered in the European patented formulation. Quercetin and Rutin with other constituents in this formulation would possibly cause potential intra- herb interaction. In this study, we have investigated the pharmacokinetic behaviour of Quercetin and Rutin from this formulation by *in vivo* pharmacokinetics in rats. The bioavailability of Quercetin was lowered from the polyherbal formulation when compared with the co-administration, whereas the Rutin bioavailability was increased from the polyherbal formulation when compared with the co-administration. Absorption of Quercetin and Rutin occurred from the different parts of the gastrointestinal tract and inter individual variation in the absorption of Quercetin from Rutin, but not from quercetin aglycone was considerable.

Also an effective pharamcokinetic (PK) and Pharmacodynamic (PD) model was established to determine the relationship between drug concentration and efficacy. PK-PD correlation allows understanding of the meaning of blood toxicant concentration and thus improve its clinical use. PD of Diabetic formulation was investigated by Streptozotocin (STZ) induced experimental diabetes. PK studies were carried out for the optimal dose determined by PD activity in plasma and analyzed by validated HPLC-MS method for PK parameters.

The PK/PD Correlations are explained by the maximum effect model ($E_{\text{max}}$) that correlates pharmacological response to drug concentrations was used to determine the maximum effect and the drug concentration that produces 50% maximum pharmacologic effect. The results in the study show that there is a relationship between Mangiferin
plasma concentrations from this formulation to responses of blood glucose containing polyherbal formulation. These evidences prompted us to speculate the possible mechanism of action of this formulation like Metformin showing extra pancreatic actions and the other possible pancreatic mechanism like glibenclamide, i.e stimulating insulin release from the pancreatic β-cells might contribute in improving oral glucose tolerance in the glucose –loaded diabetic rats and management of the diabetic condition by preventing the further changes in metabolic and regulatory mechanisms.

The present study may be concluded that, to improve the bioavailability of the biomarkers from the polyherbal formulation rather than capsule formulation, new kinds of pharmaceutical preparations or other routes of administration may be adopted. Thus the study on the pharmacokinetics of herbal medicine was very much vital in the present scenario to know its safety assessment and pharmacodynamic correlation. It is also mandatory for the regulatory purposes to produce in it as a drug status in the global market.