CHAPTER 3

REVIEW OF LITERATURE

3.1 LITERATURE REVIEW ON THE DIABETIC D- POLYHERBAL FORMULATION

The U.S. Patent and Trademark Office recently issued U.S. Patent No. 8,337,911 B2 which is entitled “Herbal formulation for the prevention and management of Type-2 Diabetes mellitus and vascular complications associated with diabetes”. This patent was assigned to SRM University, Kattankulathur, India contains claims for treatment of the vascular complications associated with type-2 diabetes mellitus consisting essentially of a therapeutically effective amount of a hydroalcoholic extract of Salacia roxburghii, Salacia oblonga, Garcinia indica and Lagerstroemia parviflora.

Osamu Muraoka et al., (2013) has carried out the quantitative determination of potent α-glucosidase inhibitors, salacinol and kotalanol, in Salacia species using liquid chromatography-mass spectroscopy. The optimum conditions of separation and detection of these two constituents were achieved on a Asahipak NH 2P-50 column with a CH 3CN–H 2O mobile phase, associated with MS using electrospray ionization source. The method was applied to evaluate extracts of three kinds of Salacia species, i.e. S. reticulata, S. oblonga, and S. chinensis, and those of four different parts, i.e. roots, stems, leaves and fruits of the same material, revealing that the extract from the roots of S. reticulata had the highest contents of these compounds. The results indicated that the assay was reproducible and precise and could be readily utilized for the evaluation of Salacia species. [32]

Maria Dolores Giron et al., (2009) has evaluated the antidiabetic properties of Salacia oblonga extract are mediated by inhibiting intestinal α-glycosidase also by enhancing glucose transport in muscle and adipose cells. S.oblonga extract effects on 2-deoxy D-glucose uptake were assayed in muscle L6-myotubes and 3t3-adipocytes. In L6-myotubes, the amount and traslocation of glucose transporters were assayed. Also they analyzed the phosphorylation status of key compounds of signaling pathways that are
involved in the molecular mechanisms regulation glucose uptake. *S. oblonga* extract increased 2-deoxy-d-glucose uptake by 50% in L6-myotubes and 3T3-adipocytes. In L6-myotubes, the extract increased up to a 100% the GLUT4 content, activating GLUT4 promoter transcription and its translocation to the plasma membrane. Mangiferin was identified as the bioactive compound. Furthermore, Mangiferin effects were concomitant with the phosphorylation of 5′-AMP-activated protein kinase without the activation of PKB/Akt. The effect of Mangiferin on 2-deoxy-d-glucose uptake was blocked by GW9662, an irreversible PPAR-γ antagonist. [33]

**Angela L. Collene et al., (2005)** has evaluated the postprandial glycemic, insulineic, and breath hydrogen responses to a liquid nutritional product containing *Salacia oblonga* extract, an herbal α-glucosidase inhibitor, and two insulinogenic amino acids. In a randomized, double-masked, crossover design, 43 healthy subjects were fed the following meals on separate days after overnight fasting: control (C; 480 mL of a study beverage containing 82 g of carbohydrate, 20 g of protein, and 14 g of fat), control plus 3.5 g each of phenylalanine and leucine (AA), control plus 1000 mg of *S. oblonga* extract (S), and control plus S and AA (SAA). Postprandially, fingerstick capillary plasma glucose and venous serum insulin levels were measured for 180 min, and breath hydrogen excretion was measured for 480 min. The baseline-adjusted peak glucose response was not different across meals. *Salacia oblonga* extract is a promising nutraceutical ingredient that decreased glycemia in this study. Supplementation with amino acids had no significant additional effect on glycemia. [34]

**Akanksha Mishra et al., (2006)** has investigated the antioxidant activity of *Garcinia indica* (kokam) and its syrup. The antioxidant activity of aqueous and boiled extracts corresponding to their use in cooking and home remedies, besides the commercial kokam syrup. The assays employed are ORAC, FRAP, ABTS and the ability to inhibit lipid peroxidation in rat liver mitochondria. Kokam syrup and the two aqueous extracts had significant antioxidant effects in the above assays. They have high ORAC values (29.3, 24.5 and 20.3), higher than those reported for other spices, fruits and vegetables. Also suggested that the high antioxidant activity of kokam adds one more positive attribute to its known medicinal properties and hence its use in cooking, home remedies and as a soft drink may be promoted. [35]
Jena BS et al., (2002) has reported that (-)-Hydroxycitric acid [(-)-HCA] is the principal acid of fruit rinds of *Garcinia cambogia*, *Garcinia indica*, and *Garcinia atroviridis*. (-)-HCA was shown to be a potent inhibitor of ATP citrate lyase, which catalyzes the extra mitochondrial cleavage of citrate to oxaloacetate and acetyl-CoA oxaloacetate. The inhibition of this reaction limits the availability of acetyl-CoA units required for fatty acid synthesis and lipogenesis during a lipogenic diet, that is, a diet high in carbohydrates. Extensive animal studies indicated that (-)-HCA suppresses the fatty acid synthesis, lipogenesis, food intake, and induced weight loss. In vitro studies revealed the inhibitions of fatty acid synthesis and lipogenesis from various precursors. [36]

Kirana H et al., (2010) has investigated the aqueous extract of *Garcinia Indica* Choisy restores glutathione in Type 2 Diabetic rats. Aqueous extract of *Garcinia indica* at a dose of 100 mg/kg and 200 mg/kg was given orally to streptozotocin-induced type 2 diabetic rats for a period of 4 weeks. At the end, parameters such as fasting blood glucose, postprandial blood glucose, and GSH in blood were analyzed. Aqueous extract of *G. indica* significantly decreased both the fasting and postprandial blood glucose in type 2 diabetic rats. The extract also restored the erythrocyte GSH in type 2 diabetic rats. Drug at higher dose, i.e. 200 mg/kg, had a more pronounced effect. Restoring the erythrocyte GSH, an intracellular anti-oxidant in diabetes, will be beneficial specially by preventing the risk of developing complications. [37]

Mazumber A et al., (2002) has carried out the phytochemical observation on leaf of *Lagestroemia parviflora* (roxb). They revealed the presence of phytosterols, tannins, alkaloids, glycosides and absence of saponin, flavonoid and triterpenoids. The phytochemical tests reveal the presence of phytosterols in all the extracts except the aqueous extract. Glycosides are present in the benzene and methanoilc extract of the leaves. Alkaloids are present in both methanolic and chloroformic extract. Tannin was sound to be present in the methanolic extract. Flavonoid, triterpenoids and saponins are absent in all the five tested extracts. [38]

Song JL et al., (2013) has investigated protective effects of *Lagerstroemia speciosa* on 3-morpholinosyndonimine (SIN-1)- induced oxidative stress in HIT-T15 pancreatic β cells. the cytoprotective effects of hot water extracts from *Lagerstroemia speciosa* leaves (LWE) on 3-morpholinosydonimine (SIN-1)-induced oxidative damage in Syrian hamster
pancreatic insulinoma HIT-T15 cells. The HIT-T15 cells were first treated with SIN-1 (50 µM) for 24 h and then co-incubated with LWE for 48 h. SIN-1 significantly decreased HIT-T15 cell viability (P<0.05); however, LWE did not exert a significant cytotoxic effect and increased the viability of HIT-T15 cells in a dose-dependent manner. These results suggest that LWE has a cytoprotective effect against SIN-1-induced oxidative stress in HIT-T15 cells through the inhibition of lipid peroxidation, a decrease in ROS levels and an increase in antioxidant enzyme activity. In addition, LWE increased insulin secretion in SIN-1-treated HIT-T15 cells. Also the results suggested that LWE were effective in the treatment of diabetes. [39]

Hou W et al., (2009) has isolated the triterpene acids from Lagerstroemia speciosa leaves as alpha-glucosidase inhibitors. The potential antidiabetic activity of ethyl acetate extract of the leaves of Lagerstroemia speciosa (LSL) was investigated by alpha-amylase and alpha-glucosidase inhibition assay. Six pentacyclic triterpenes (oleanolic acid, arjunolic acid, asiatic acid, maslinic acid, corosolic acid and 23-hydroxyursolic acid) were isolated from LSL. Their structures were determined by spectroscopic analysis and their alpha-glycosidase and alpha-amylase inhibitory activities were investigated. They exhibited no or weak inhibitory activity against alpha-amylase and middle alpha-glucosidase inhibitory activities. Corosolic acid, which shows best bioactivity against alpha-glucosidase (IC(50) = 3.53 microg/mL), contributes most to the alpha-glucosidase inhibitory activity of EtOAc extract. The kinetics of inhibition of corosolic acid was also discussed. Results from this study might provide the scientific evidence for LSL for the treatment of diabetes in traditional medicine. [40]

3.2 LITERATURE REVIEW ON NEURODEGENERATIVE N-POLYHERBAL FORMULATION

The European Patent Office recently issued European Patent No. 1569666B1 which is entitled “Herbal formulation for management of cardiovascular and neurologic disorders”. This patent was assigned to Banaras Hindu University, Varanasi, India contains claims for treatment of management of cardiovascular and neurologic disorders and to a process of the preparation there of. According to this invention the polyherbal formulation
comprising of three constituents namely *Dioscorea bulbifera*, *Hippphoe rhamnoides* and *Bacopa monnieri*.

**Manisha Rastogi et al., (2011)** has investigated on the prevention of age-associated neurodegeneration and promotion of healthy brain ageing in female Wistar rats by long term use of bacosides. The neuroprotective effect of bacosides, the active saponins of Bacopa monnieri (L.) against age associated neurodegeneration and its impact over the prevention of Senile Dementia of Alzheimer’s Type (SDAT). The optimum dose of bacosides with no adverse effect was selected by screening its dose dependant activity on ageing biomarker lipofuscin and SDAT biomarker neuro-transmitter acetylcholine in the aged female Wistar rat brain. Bacosides may act as a potential therapeutic intervention in forestalling the deleterious effects of ageing and preventing the age associated pathologies like SDAT. [41]

**Pooja Jadiya et al., (2011)** has carried out the anti-parkinsons effects of Bacopa monnieri from transgenic and pharmacological *Caenorhabditis elegans* models of Parkinson’s disease. Two different strains of C. elegans; a transgenic model expressing “human” alpha synuclein [NL5901 (Punc-54::alphasynuclein::YFP+unc-119)], and a pharmacological model expressing green fluorescent protein (GFP) specifically in the dopaminergic neurons [BZ555 (Pdat-1:GFP)] treated with selective catecholaminergic neurotoxin 6-hydroxy dopamine (6-OHDA), were employed for the study. B. monnieri was chosen for its known neuroprotective and cognition enhancing effects. The study examined the effect of the botanical, on aggregation of alpha synuclein, degeneration of dopaminergic neurons, content of lipids and longevity of the nematodes. These studies show that B. monnieri reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent [42].

**Lamiaa A et al., (2014)** has studied on the role of oxidative stress, inflammation, nitric oxide and transforming growth factor-beta in the protective effect of diosgenin in monocrotaline-induced pulmonary hypertension in rats. Pulmonary hypertension was induced by a single subcutaneous injection of monocrotaline (60 mg/kg). Diosgenin (100 mg/kg) was given by oral administration once daily for 3 weeks. At the end of the
experiment, mean arterial blood pressure, electrocardiography and echocardiography were recorded. Rats were then sacrificed and serum was separated for determination of total nitrate/nitrite level. Right ventricles and lungs were isolated for estimation of oxidative stress markers, tumor necrosis factor-alpha, total nitrate/nitrite and transforming growth factor-beta contents. Myeloperoxidase and caspase-3 activities in addition to endothelial and inducible nitric oxide synthase protein expression were also determined. Moreover, histological analysis of pulmonary arteries and cardiomyocyte cross-sectional area was performed. Diosgenin treatment provided a significant improvement toward preserving hemodynamic changes and alleviating oxidative stress, inflammatory and apoptotic markers induced by monocrotaline in rats. Furthermore, diosgenin therapy prevented monocrotaline-induced changes in nitric oxide production, endothelial and inducible nitric oxide synthase protein expression as well as histological analysis. [43]

Sarmistha Saha et al., (2014) has isolated diosgenin and prevents the calcium oxalate-induced apoptotic death and oxidative stress in MDCK cells. Diosgenin was isolated from fruits of Solanum xanthocarpum by silica gel column chromatography. It was obtained in high yields (1.23%) and the purity was ascertained by HPTLC analysis. Characterization of diosgenin was done by mp, UV–visible spectrophotometry, elemental analysis, FT-IR, $^1$H NMR and $^{13}$C NMR analysis. Cells were co-incubated with COM (80 μg/cm²) and diosgenin (2.5, 5, 7.5 and 10 μg/mL) for 24 h. It was found that diosgenin attenuated the apoptotic death induced by COM as measured in terms of cell viability, caspase -9/3 activities and DNA fragmentation percent. The inhibitory role of diosgenin on caspase -9/3 activities was also analyzed using molecular docking experiments, which showed interactions to their active sites by H-bonds. Diosgenin also attenuated the increase in lipid peroxidation and glutathione depletion induced by COM crystals. They concluded, the preventive effect of diosgenin is associated to the inhibition of oxidative stress and caspases. [44]

Rana Gopal Singh et al., (2013) has studied the Immunomodulation and antiproteinuric effect of Hippophae rhamnoides (Badriphal) in idiopathic nephrotic syndrome. The study had 2 groups having 28 patients of idiopathic nephrotic syndrome in each group have been included. The patients were subjected to haematological, biochemical, immunological investigation at 0, 1, 2 and 3 months interval with dietic advice. Group A
have been put on standard treatment, whereas group B on Badriphal in the well worked up doses. The hydroalcoholic extract of 350 mg twice daily of Badriphal was given to group B as add on treatment. Patients were followed up with definite protocol at monthly interval for 3 months. At the end of 3 month patients showed improvement in the symptoms of oedema, anorexia, oliguria in the herbal group. The urinary estimation of protein showed significant decrease in Group B with elevation of S. albumin levels. The inflammatory cytokines has showed significant decrease at the end of 3 month. This the pilot study showed beneficial effect of the herbal preparation Hippophae rhamnoides as add on treatment. [45]

Geetha S et al., (2003) has evaluated antioxidant activity of leaf extract of Seabuckthorn (Hippophae rhamnoides L.) on chromium (VI) induced oxidative stress in albino rats. Oxidative stress was induced in the rats by force-feeding of potassium dichromate equivalent to a dose of 30mg/kg body weight (BW) of chromium(VI) for 30 days. Administration of chromium decreased the body weight and increased organ to body weight ratio significantly. Chromium treatment significantly decreased reduced glutathione (GSH), and increased malondialdehyde (MDA) and creatine phosphokinase (CPK) levels; further it also enhanced glutamate oxaloacetate transferase (GOT) and glutamate pyruvate transferase (GPT) levels in the serum. Different doses of the alcoholic leaf extract of Seabuckthorn were evaluated for the protection against the chromium induced oxidative stress. The results show that the leaf extract at a concentration of 100 and 250mg/kg BW protected the animals from the chromium induced oxidative injury significantly. [46]

3.3 LITERATURE ON THE STANDARDIZATION AND QUALITY CONTROL OF HERBAL FORMULATIONS

Tekeshwar Kumar et al., (2011) has standardized the Gokshuradi Churna – An Ayurvedic polyherbal formulation. This traditional drug more stable for long term storage and hence, easier to prepare. It is used as diuretic and cardiac tonic. One marketed and one in-house formulations were used for the study. All the formulations were standardized on the basis of organoleptic characters, physical characteristics and physico-chemical properties. The set parameters were found to be sufficient to evaluate the churna and can be used as reference standard for the quality control/quality assurance purposes. The analysis and quality control of herbal medicines are moving towards an integrative and
comprehensive direction, in order to better address the inherent holistic nature of herbal medicines. It was observed that, all ingredients of commercial samples matched exactly with that of authentic standards after performing the standardization as per WHO guideline. [47]

**Abhishek Bharadwaj et al., (2014)** discussed the characterization, phytochemical determination of antilithiac polyphyto dispersible tablet. They made an attempt to standardize polyphyto dispersible tablet by using macroscopy characteristics and microscopy characters, powder microscopy, fluorescence analysis, quantitative and physiochemical values. The proper examination of the polyphyto combinations was carried out under sunlight and artificial source similar to daylight. The data reveals that phytotherapeutic agents could be useful as either an alternative or complementary therapy in the management of urolithiasis. [48]

**Rasheed et al., (2010)** has standardized a compound of Unani herbal formulation “Qurs-e- Luk” with modern techniques. The drug is widely used in Unani system of medicine for mobilizing and reducing body fat, which is Istisqae- Lehmi in terms of Unani Medicine. It is also very effective tonic for liver and diuretic. In order to standardize and to lay down the standard operating procedures (SOPs) and pharmacopoeial standards, the formulation was prepared in three batches at laboratory scale. It was subjected to analysis for microscopic studies, physicochemical parameters, microbial load, heavy metals, aflatoxins, pesticide residues and high-performance thin layer chromatographic studies. [49]

**Makhija IK et al., (2012)** has standardized an ayurvedic formulation Sitopaladi churna. They have done the physio-chemical standardization of in-house and two marketed brands of Sitopaladi churna. They were standardized based a powder microscopy, physicochemical evaluations, Thin layer chromatography and High performance thin layer chromatography finger printing as per standard procedures. The data evolved can be adopted for laying sdown the standards for the manufacturing units of Sitopaladi churna. [50]

**Sriwastava NK et al., (2010)** has standardized a polyherbal formulation Ajmodadi churna. It is a polyherbal ayurvedic medicine, used as carminative and antispasmodic and is a strong wormifuge helps in all painful conditions like sciatica and stiffness in back and also restores normal digestive functions. Ajmodadi churna was prepared as per Ayurvedic Formulary of India. In-house preparation and the marketed drug have been standardized on the basis of organoleptic characters, physical characteristics and physico-chemical
properties. A set parameters were found to be sufficient to evaluate the churna and can be used as reference standards for the quality control/quality assurance laboratory of a Pharmaceutical house. [51].

**Ladva BJ et al., (2014)** has done the marker based standardization of polyherbal formulation (SJT-DI-02) by high performance thin layer chromatography method. The work was marker based standardization of patented, novel and efficacious polyherbal formulation namely SJT-DI-02 for the treatment of diabetes. The SJT-DI-02 was comprised of dried extracts of rhizomes of *Acorus calamus*, leaves of *Aegle marmelose*, fruits of *Benincasa hispida*, roots of *Chlorophytum arendinaceum*, seeds of *Eugenia jambolana*, leaves of *Ocimum sanctum*, pericarp of *Punica granatum* and seeds of *Tamarindus indica*. The formulation was prepared by mixing different fractions of extracts. Selection is done on the basis of therapeutic efficacy and amount of marker present in the particular plant part. Phytochemical screening and estimation of phytoconstituents was carried out. After completion of preliminary screening using characterized markers, developed TLC systems using selected solvent composition. The polyherbal formulation was standardized by using different four markers. % w/w of asarones is 3.61, % w/w of marmelosin is 4.60, % w/w of gallic acid is 10.80 and % w/w of lupeol is 4.13. Thus high performance thin layer chromatography (HPTLC) methods were developed and validated in terms of linearity, precision, repeatability, limit of detection, limit of quantification and accuracy. The method was rapid, sensitive, reproducible and economical. This work provides standardized and therapeutically active polyherbal formulations for various ailments. [52]

**Shivani Chauhan et al., 2013** has carried out the pharmacopeial standardization of polyherbal formulation mahasudharshan churna. It is currently used as diaphoretic and antimalarial. It is also useful in dyspepsia and loss of appetite. It was standardized in order to assess the quality of drugs, based on the concentration of their active principles according to world health organization guidelines. The various parameters performed includes organoleptic characteristics and physicochemical characteristics. The set parameters were found to be sufficient to standardize the Mahasudarshan churna and can be used as reference standards for the quality control/ quality assurance study mostly on plant drugs for their primary health care needs. The results obtained may be considered as tools for assistance to
the regulatory authorities, scientific organization and manufacturers for developing standard formulation of great efficacy. [53]

**Pallab Das Gupta et al., (2012)** has developed the standardization parameters of Gita Pachak Haritaki – A polyherbal formulation. It contains eight herbal ingredients and used in the treatment of indigestion, constipation and to improve appetite. The formulation has been standardized on the basis organoleptic characters, Physico-chemical parameters, TLC and heavy metals study. The study shows that, the contents of formulation presents within the permissible limits as per WHO, all these investigations are not specified in the standard literature such as in pharmacopoeia, which could helpful in authentication of Gita Pachak Haritaki. [54]

### 3.4 LITERATURE ON THE PHARMACODYNAMIC ACTIVITY OF HERBAL FORMULATIONS

**Srinivasan Prabhu et al., (2014)** has investigated antidiabetic, hypolipidemic and histopathological analysis of *Gymnema sylvestre* methanolic extract (GSME) in streptozotocin induced diabetic rat by administering oral doses (100, 200 and 400mg mg/kg body weight). Blood glucose levels were measured using blood glucose test strips with elegance glucometeron weekly intervals till the end of the study (i.e. four weeks). Blood glucose, urine sugar, triglycerides (TG), Low density lipoprotein (LDL), high density lipoprotein (HDL) and very low density lipoprotein (VLDL) were determined in normal and streptozotocin induced diabetic rats after oral administration of the extract for 28 days. Histopathological changes in diabetic rat organs (pancreas, liver and kidney) were also observed, after extract treatment. Daily oral administration of GSME (100, 200 and 400 mg/kg body weight) and Glibenclamide(5 mg/kg) showed beneficial effects on blood glucose level (P < 0.01) and hyperlipidaemia due to diabetes. The extract treatment also showed to enhance serum insulin level and body weight of diabetic rats as compare to diabetic control group. *G. sylvestre* possesses antidiabetic property as well improve body weight, and total lipid levels. GSME has also favorable effect to inhibit the histopathological changes in streptozotocin-induced diabetes. [55]

**Hansi Misbah et al., (2013)** has investigated the antidiabetic and antioxidant properties of *Ficus deltoidea* fruit extracts and its fractions. Two fruit varieties of F.
deltoidea (var. angustifolia (SF) and var. kunstleri (BF)) were extracted separately using double-distilled water. The resulting aqueous extracts were partitioned using ethyl acetate to obtain the ethyl acetate and water fractions. Antidiabetic activity were assessed based on the ability of the samples to inhibit yeast and mammalian $\alpha$-glucosidase as well as $\alpha$-amylase. Antioxidant capacities were examined by measuring the ability of the samples to reduce ferric ions and to scavenge DPPH, superoxide anion, ABTS and nitric oxide radicals. The crude extracts and fractions of SF and BF inhibited both yeast and rat intestinal $\alpha$-glucosidase in a dose-dependent manner, but does not inhibit porcine pancreatic $\alpha$-amylase. The water fraction of BF showed the highest percentage of $\alpha$-glucosidase inhibition while having the highest amount of protein (73.33 ± 4.99 μg/mg fraction). All the extracts and fractions exhibited antioxidant activity, with SF crude extract showing the highest antioxidant activity with phenolic content (121.62 ± 4.86 mg/g of extract). Fractionation of the crude extracts resulted in loss of antioxidant activity. There was no positive correlation between phenolic and flavonoid content with $\alpha$-glucosidase inhibitory activities. The study the compounds possessing both antihyperglycemic and antioxidant activities may provide a new approach in the treatment of diabetes mellitus. [56]

Parminder Nain et al., (2012) et al has reported antidiabetic and antioxidant potentials of Emblica officinalis Gaertn. Leaves extract in streptozotocin-induced type – 2 diabetes mellitus (T2DM) rats. The hypoglycemic effect was measured by blood glucose and plasma insulin level. The oxidative stress was measured in liver and kidney by level of antioxidant markers i.e. lipid peroxidation (LPO), superoxide dismutase (SOD), reduced glutathione(GSH), glutathione peroxidase (GPx) and catalase (CAT) and the biochemical parameters, i.e. blood serum levels of creatinine, urea, serum glutamic pyruvic transaminases (SGPT), serum glutamic oxaloacetic transaminases (SGOT), alkaline phosphatase (ALP), total cholesterol and triglyceride levels were the salient features observed in diabetic control and treated rats. Oral administration of the Emblica officinalis at a concentration of 100, 200, 300 and 400mg/kg b.w. daily for 45days showed a significant decrease in fasting blood glucose and increase insulin level as compared with the diabetic rats. The results clearly suggest that the hydromethanolic extract of leaves of Emblica officinalis Gaertn treated group may effectively normalize the impaired antioxidant status in
Sheng-Zi Liu et al., (2013) has carried out the anti-diabetic effect of traditional Chinese scutellaria-coptis herb extract (SC) and its main components. Also they explore its mechanism from the effect on intestinal disaccharidases by in vivo and in vitro experiment. SC extract was prepared and the main components (namely berberine and baicalin) contained in the extract were assayed using high performance liquid chromatography (HPLC). Diabetic model rats were induced by intraperitoneal injection of streptozotocin (STZ). After randomly grouped, diabetic rats were administered SC extract, berberine, baicalin, acarbose and vehicle for 33 days respectively. Body weight, food intake, urine volume, urine sugars, fasting plasma glucose and fasting plasma insulin were measured to evaluate the antidiabetic effects on diabetic rats. After the treatment of SC extract and its main components, the body weight and the fasting plasma insulin level were increased while food intake, urine volume, urine sugars and fasting plasma were decreased. OGTT showed that, SC extract and its main constituents could lower the postprandial plasma glucose level of diabetic rats. According to present findings, Scutellaria coptis herb couple (SC) possessed potent anti-hyperglycemic effect on STZ-induced diabetic rats via inhibiting the increased activities of intestinal disaccharidases and elevating the level of plasma insulin. [58]

3.5 LITERATURE REVIEW ON THE PHARMACOKINETICS OF HERBAL FORMULATIONS

Jue song et al., (2012) has evaluated the pharmacokinetic – pharmacodynamic correlation of the major component Astragaloside IV on the immunomodulatory effects of YU-ping-feng prescription. Yu-ping-feng decoction (YPF), a traditional Chinese medicine (TCM) prescription, is widely used to treat some respiratory tract diseases. YPF administration were tested on spleen cells of rats in vitro and proliferation ratio of spleen cell was used as an end point to evaluate pharmacodynamic properties of immunoregulatory effects of YPF prescription. With HPLC–MS method, concentrations of Astragaloside IV (AS), a main component of YPF, was determined to achieve pharmacokinetic parameters after administration of a simplified prescription which is composed with AS, Astractylenolide I and Prim-o-glucosylcimifugin, which are representative components of
YPF. A plot of serum AS concentration versus time and effects showed that, there was a positive relationship between AS concentrations and effects of YPF, and the concentration–response curve which was based on an $E_{\text{max}}$ model showed a counterclockwise hysteresis manner. A PK–PD model with Sheiner’s method was used to describe time course of AS concentration in blood compartment and effect compartment, and main parameters with the PK–PD model were calculated. These results showed that there is a symmetry relationship between serum AS concentrations and responses of serum containing medicine of YPF prescription, which means that AS plays an important role in immunoregulatory effects of YPF. The investigation on dose–effect relationships has displayed a feasible method to clarify mechanisms of combination for TCM prescriptions. [59]

**Chang-Hua Xu et al., (2013)** has investigated the comparative pharmacokinetics of ten bioactive compounds in Shaoyao-Gancao Decoction (SGD) with two different combinations of *Radix paeonia Alba* and *Glycyrrhiza uralensis* to study the herb-herb interaction mechanisms of SGD for better spasmolysis and emergency pain relief in rats by oral administration of two different combinations equivalent to 9.5g/kg body weight of *Glycyrrhiza uralensis* (GU).The results indicated that the increasing amount of the *Radix paeonia* Alba attenuated the inhibitory effect of glycyrrhetinic acid via competing consumed by intestinal bacteria to reduce the conversion amount of glycyrhizin to glycyrrhetinic acid and subsequently to afford significantly higher bioavailability and longer efficacy of other glycosides leading to better spasmolysis and emergency pain. [60]

**Hao Wu et al., (2009)** has carried out the comparative pharmacokinetic study of paeoniflorin after oral administration of pure paeoniflorin, extract of *Cortex moutan* and Shuang-Dan prescription to rats at a dose of 30 mg/kg paeoniflorin. At different time points plasma concentration of paeoniflorin was determined using a simple and rapid HPLC–MS method. A bimodal phenomenon was observed, in the plasma profile after oral administration of *Cortex moutan* extract. The investigation showed that, among all calculated parameters, $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$, $\text{MRT}$, $K_e$ and $T_{1/2}$, there was no significant difference between the two decoctions. The results indicated that the reason which delay the elimination of paeoniflorin and enhances its bioavailability might be some of the ingredients present in *Cortex moutan* extract. [61]
Shaoying Hou et al., (2012) investigated the pharmacokinetics of Mangiferin in human by developing a sensitive high performance liquid chromatography–mass spectrometry (HPLC–MS) method for the determination of Mangiferin in human plasma. The proposed HPLC–MS method is selective, precise and accurate enough and enable to identify and quantify Mangiferin for the use in clinical studies. After single oral administration of 0.1, 0.3 and 0.9 g of Mangiferin, respectively, the method was successfully applied for the pharmacokinetics of Mangiferin in 21 healthy male Chinese volunteers. The pharmacokinetics of Mangiferin was fit to be non-compartmental model. Mangiferin concentration in plasma reached 38.64 ± 6.75 ng/mL about 1 h after oral administration of 0.9 g of Mangiferin and the apparent elimination half-life (T_{1/2}) was 7.85 ± 1.72 h. The absorption of Mangiferin was increased with the administration of a large dose and it was concluded that, the pharmacokinetics of Mangiferin in human was non-linear. [62]

Sampath et al., (2012) reported the, pharmacokinetics of valerenic acid in rats after intravenous and oral administrations. Valerenic acid in rat plasma was biphasic, subdivided in fast distribution and a slow elimination phase. The half-life of the distribution phase was 6-12 min and that of the terminal elimination phase of 6-64 h, indicating a possible large tissue binding. Disposition pharmacokinetics of Valerenic acid after oral treatment was also described by two compartmental model with a clearance (CL/F) of 2-5L h^{-1}.The extent of absorption after oral administration was estimated to be 33.70% with a half-life of 2.7-5h. Dose proportionality was observed in terms of dose and AUCs, suggesting linear pharmacokinetics at the dose level studied in rats. [63]

Chun-Yong He et al., (2012) has investigated the pharmacokinetics, tissue distribution and metabolism of senkyunolide I, a major bioactive component in Ligusticum chuanxiong Hort.(Umbelliferae). The concentration of senkyunolide I in plasma and tissues were determined by a high performance liquid chromatography (HPLC) method and the pharmacokinetics parameters were calculated using non-compartmental model. The results indicated, that the senkyunolide I was quickly eliminated from plasma and its oral bioavailability was about 37.25% which was smaller then intraportal bioavailability 81.17%, but similar to intraduodenal bioavailability 36.91% suggesting that, gastric first pass effect of senkynolide I is negligible and heaptic first pass effect was approximately 18.83%. The
metabolic mechanism of Senkyunolide I in rat mainly involves methylation, glucoronidation and glutathione conjugation during the phase II biotransformation pathway in rats. [25]

Jian feng Xing et al., (2011) carried out the metabolic pharmacokinetic studies of scutellarin in rat plasma, urine and feces. A single oral dose of scutellarin (400 mg/kg), the plasma concentration of scutellarin and scutellarein in female rats were significantly higher than in male ones. Between the female and male rats, significant differences in AUC, T_{max} and C_{max} for scutellarin were found. The total percentage excretion of scutellarin and scutellarein in the feces was higher with oral administration than with intravenous administration. The in vitro T_{1/2} and CL_{int} value for scutellarin in male rats were significantly higher, than that of female rats. The results suggest that, a large amount of ingested scutellarin was metabolized into scutellarein in the gastrointestinal tract and then excreted with the feces, leading to extremely low oral bioavailability of scutellarin. The gender differences of pharmacokinetic parameters of scutellarin and scutellarein are due to the higher CL_{int} and lower absorption in male rats. [64]

Qin Zheng et al., (2011) carried out the pharmacokinetics study of a novel Chinese traditional formula and its compatibility. Da Chuan Xiong decoction compound preparation (DCXDCP), the formulation of a classical Chinese prescription recorded in “Xuanminglunfang”, which was clinically employed to treat migraine’s disease was investigated the influence of compatibility on the pharmacokinetics of the active ingredient gastrodin (GAS), with various combinations of its constituent herbs in plasma after oral administration. The pharmacokinetic parameters, AUC and C_{max} of GAS were dramatically different (p < 0.05) after oral administration of Gastrodia elata BL. and the different combinations of its constituent herbs. The compatibility effects of other ingredients present in DCXDCP could affect the pharmacokinetics of the prescription. [65]

Guowen et al., (2012) investigated on the pharmacokinetics properties of Isorhamnetin, Kaempferol and Quercetin after oral gavage of total flavones of Hippophae rhamnoides L. in rats using a UPLC–MS method. The pharmacokinetic parameters of Isorhamnetin, Kaempferol and Quercetin from TFH in rats were quantitatively determined by UPLC with photodiode array detection (PDA). The qualitative detection of the three flavone was accomplished by selected ion monitoring in negative ion mode ESI-MS. Results
of the pharmacokinetic study indicate that, the three flavones in TFH were absorbed by passive diffusion in rats, and no “double-peak” phenomenon was observed in C-t curves of the three flavones from TFH except for Quercetin. [66]