## CONTENTS

### 1. INTRODUCTION

1.1 Quality control and standardization of HDs: Marker and Fingerprint based approach
1.2 Pharmacokinetics of HDs: Bioactives and plasma phytopharmacology approach
1.3 Herb-drug and/or drug-herb interactions: *In silico*, *in vitro* and *in vivo* approach
1.4 Scope of proposed investigation: *Gymnema sylvestre* as case example

### 2. REVIEW OF LITERATURE

2.1 Quality control and modern standardization tools
2.2 Pharmacokinetics and bioavailability of natural products
2.3 Approaches to overcome poor bioavailability issues of herbal drugs
2.4 Herb-drug interactions
   - 2.4.1 Pharmacodynamic interactions
   - 2.4.2 Pharmacokinetic interactions
2.5 PLANT PROFILE (*Gymnema sylvestre*)
2.6 REFERENCE DRUGS PROFILE
   - 2.6.1 Glimepiride
   - 2.6.2 Metformin
2.7 PROFILE OF POLYMERS
   - 2.7.1 Chitosan
   - 2.7.2 Poly (lactic-co-glycolic acid) (PLGA)

### 3. SCOPE AND OBJECTIVES

### 4. MATERIALS AND METHODS

4.1 Quality control and standardization of *G. sylvestre* extract: Quantitative estimation of GMG from various *G. sylvestre* formulations and extract using HPLC-ESI-MS/MS as a quality control tool
4.2 Isolation, purification and characterization of GMG from *G. sylvestre* extract.
4.3 Evaluation of acute oral toxicity of *G. sylvestre* extract and GMG as per OECD 423 guidelines.
4.4 Determination of absolute bioavailability of GMG after oral and iv administration in normal rats.
4.5 Development, optimization & characterization of *G. sylvestre* extract and GMG loaded polymeric nanoparticles.
4.6 Evaluation of comparative bioavailability of developed polymeric nanoformulations with GMG and *G. Sylvestre* extract.
4.7 Preparation & characterization of sodium and potassium salts of isolated GMG.
4.8 Evaluation of comparative anti-hyperglycemic potential of GMG, its sodium, potassium salts, and nanoparticles with *G. sylvestre* extract in streptozotocin induced diabetic rats.
4.9 *In vitro* cytotoxicity evaluation of GMG using MTT assay.
4.10 Herb-drug interaction studies of *G. sylvestre* extract with selected conventional drug, glimepiride.

5. **RESULTS AND DISCUSSION**

5.1 Quality control and standardization of *Gymnema sylvestre* extract and its marketed formulations.
   5.1.1 Optimization of mass spectrometry and chromatography conditions
   5.1.2 Method Validation
   5.1.3 Method Applicability

5.2 Isolation, purification and characterization of GMG from *Gymnema sylvestre* extract.
   5.2.1 Isolated GMG and its Characterization
   5.2.2 Mass spectral analysis of isolated GMG
   5.2.3 NMR spectral analysis of isolated GMG

5.3 Acute oral toxicity study of *Gymnema sylvestre* extract and GMG as per OECD 423 guidelines.
   5.3.1 Effect on general behaviour and mortality
   5.3.2 Effect of *G. sylvestre* extract and GMG on body weight
   5.3.3 Effect of GMG on haematological parameters
   5.3.4 Effect of GMG on the organ Histopathology (day 14)

5.4 Pharmacokinetics of bioactive phytoconstituents.
   5.4.1 Determination of absolute bioavailability of GMG after iv and oral administration in rats.
   5.4.2 Plasma sample preparation optimization
   5.4.3 Optimization of mass spectrometry and chromatography conditions
   5.4.4 Method validation
   5.4.5 Determination of absolute bioavailability of GMG

5.5 Development, optimization and characterization of *G. sylvestre* extract and GMG nanoparticles.
   5.5.1 Preformulation Studies
   5.5.2 Development of nanoparticle formulation
   5.5.3 Entrapment efficiency
   5.5.4 Stability studies
   5.5.5 *In vitro* drug release.

5.6 Determination of bioavailability of developed nanoparticles
   5.6.1 Evaluation of comparative bioavailability of *G. sylvestre* extract and its nanoparticles after oral administration in normal rats.
   5.6.2 Evaluation of comparative bioavailability of GMG and its nanoparticles after oral administration in normal rats.

5.7 Preparation & characterization of sodium and potassium salts of isolated GMG.

5.8 Evaluation of comparative anti-hyperglycemic potential of GMG, GMG nanoparticle, its water soluble salts, with *G. sylvestre* extract in STZ induced diabetic rats.
   5.8.1 Effect on blood glucose level
5.8.2 Effect of *G. sylvestre* extract, GMG, GMG salts and GMG nanoparticles on glycosylated haemoglobin (HbA1c).

5.8.3 Effect of *Gymnema sylvestre* extract, GMG, GMG salts and GMG nanoparticles on serum insulin level.

5.8.4 Effect of *Gymnema extract*, GMG, GMG salts and GMG nanoparticles on histopathology.

5.8.5 Effect of Gymnema parent extract, GMG, their nanoparticles and GMG salts on the change in body weight of animals.

5.8.6 Effect of *G.sylvestre* extract, GMG alone, their nanoparticles and GMG salts on total cholesterol (TC) and triglycerides level (TG).

5.9 *In vitro* antiproliferation screening of GMG

5.10 Herb-Drug Interaction studies of *Gymnema sylvestre* extract with selected conventional drug, Glimepiride.

5.10.1 *In silico* interaction studies of *G. sylvestre* extract.

5.10.2 To study the pharmacodynamics effect of the *Gymnema sylvestre* extract, glimepiride (GLM) and their effect on anti-hyperglycemic and anti-hyperlipidemic activities on con-comitant administration in STZ induced diabetic rat model.

5.10.3 Pharmacokinetic interactions.

6. **SUMMARY AND CONCLUSION**

7. **FUTURE DIRECTIONS**

8. **BIBILOGRAPHY**

9. **ANNEXURE**

   Annexure I (a) Certificate of analysis *Gymnema sylvestre* extract

   Annexure I (b) Certificate of analysis Gymnemagenin

   Annexure I (c) Certificate of Chitosan as Gift sample

   Annexure I (d) Certificate of analysis Metformin

   Annexure I (e) Certificate of analysis Glimepiride

   Annexure IIa Animal Ethical Clearance Form

   Annexure IIb Histopathological findings of *in vivo* anti-hyperglycemic evaluation of GMG its products and *G.sylvestre* extract.

   Annexure III Results of particle size and zeta potential

   Annexure IV List of Publications and Patents filed

Publication reprints enclosed.